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CICLO XXXVII

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DEVELOPMENT OF NEW PERSONALIZED DIAGNOSTIC AND THERAPEUTIC STRATEGIES IN GIANT CELL ARTERITIS: IDENTIFICATION OF NEW MARKERS FOR DISEASE SUBSETS AND PREDICTORS OF THERAPEUTIC RESPONSE

DOTTORANDA

Dott.ssa Francesca Regola

SUPERVISORE

Prof. Franco Franceschini

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RIASSUNTO

L'Arterite a Cellule Giganti (GCA) è una vasculite dei grandi vasi che presenta un esordio spesso insidioso, portando a ritardi diagnostici e terapeutici con conseguenti complicanze gravi. La diagnosi corretta è cruciale per impostare una terapia adeguata, che tradizionalmente si basa su glucocorticoidi (GC), non sempre efficaci e associati a un'alta incidenza di effetti collaterali. Per questi motivi, negli ultimi anni si è esplorato l'uso di immunosoppressori come Tocilizumab (TCZ).

Persistono, tuttavia, interrogativi aperti sul miglior approccio terapeutico: il futuro sembra orientato verso una medicina sempre più personalizzata ma, ad oggi, mancano biomarcatori validati.

L'attività di ricerca presentata in questa tesi ha avuto l'obiettivo di ampliare le conoscenze scientifiche sulla GCA, ponendo le basi per una futura medicina personalizzata. L'obiettivo è stato duplice: identificare i fattori di rischio per complicanze gravi di malattia e i fattori predittivi di risposta alla terapia.

Il lavoro si è articolato in quattro sezioni principali:

- Uno studio introduttivo sull'epidemiologia della GCA nel territorio di ATS Brescia, per fornire una rappresentazione della realtà clinica su cui si fondano gli studi successivi. Sono stati identificati i pazienti con diagnosi di GCA residenti in ATS Brescia utilizzando il metodo capture/recapture, unendo dati amministrativi (certificazione di malattia rara presso ATS) e dati clinici (database dei principali Ospedali). È stata identificata una media di 24 nuove diagnosi di GCA all'anno e un'incidenza media di 4,5 casi/100.000 abitanti con età maggiore di 50 anni. Non sono emerse variazioni significative nelle manifestazioni cliniche nel tempo e le caratteristiche della coorte sono risultate simili a quelle internazionali, confermando la sua rappresentatività per la popolazione affetta da GCA.
- Un'analisi dei dati della coorte storica di pazienti affetti da GCA seguiti presso l'ASST Spedali Civili di Brescia con l'obiettivo di identificare fattori prognostici di gravità (coinvolgimento dei grossi vasi, sviluppo di cecità e ospedalizzazione). I fattori di rischio per interessamento dei grossi vasi sono risultati essere l'età minore alla diagnosi e la presenza di sintomi sistemici, mentre quelli per la cecità l'età più avanzata e la presenza di maggiori comorbilità al momento della diagnosi, in particolare ipertensione e insufficienza renale cronica. I pazienti a maggior rischio

per ospedalizzazione sono risultati quelli fumatori, ipertesi, con insufficienza renale cronica e pluripatologici. La maggior parte dei ricoveri era dovuta a infezioni o complicanze cardiovascolari, suggerendo una possibile correlazione con gli effetti collaterali delle terapie steroidee e immunosoppressive.

- Un'analisi dello stato dell'arte della terapia per la GCA, con particolare attenzione agli effetti collaterali dei GC e all'effetto steroido-risparmiatore di TCZ. Il 90% dei pazienti ha sviluppato almeno un effetto collaterale e il danno indotto dai GC è risultato correlato alla dose cumulativa di GC e alla presenza di comorbidità al momento della diagnosi. L'utilizzo di TCZ ha ridotto del 25% la dose cumulativa di GC e il conseguente danno e ha ridotto il rischio di recidiva della malattia.
- Uno studio sull'identificazione di nuovi biomarcatori, analizzando il possibile ruolo di sottopopolazioni linfocitarie (Th17 e Treg), potenzialmente implicate nella patogenesi di malattia. Le cellule Th17, proinfiammatorie, sono diminuite dopo trattamento, soprattutto nei responder cioè nei pazienti che passavano da uno stato di malattia attiva a quello di inattiva. Non sono stati osservati cambiamenti significativi nelle cellule Treg, sebbene vi fosse una leggera tendenza alla riduzione.

Infine, nella sezione 2 della tesi sono raccolti progetti di ricerca dedicati ad altre vasculiti sistemiche, quali la Granulomatosi Eosinofilica con Poliangite (EGPA) e le Vasculiti ANCA associate (AVV).

SUMMARY

Giant Cell Arteritis (GCA) is a large vessel vasculitis that often presents with an insidious onset, leading to diagnostic and therapeutic delays, which can result in severe complications. Accurate diagnosis is crucial for establishing appropriate therapy, which traditionally relies on glucocorticoids (GC), often ineffective and associated with a high incidence of side effects. Consequently, recent years have seen the exploration of immunosuppressants like Tocilizumab (TCZ). However, questions remain regarding the best therapeutic approach; the future appears to lean towards increasingly personalized medicine, yet validated biomarkers are still lacking.

The research presented in this thesis aimed to expand scientific knowledge on GCA, laying the groundwork for future personalized medicine. The objectives were twofold: to identify risk factors for severe complications of the disease and predictive factors for treatment response.

The work is organized into four main sections:

- An introductory study on the epidemiology of GCA in the ATS Brescia area to provide a clinical representation that informs subsequent studies. Patients diagnosed with GCA residing in ATS Brescia were identified using the capture/recapture method, combining administrative data (rare disease certification at ATS) and clinical data (from major hospital databases). An average of 24 new GCA diagnoses per year was identified, with a mean incidence of 4.5 cases per 100,000 inhabitants over 50 years of age. No significant variations in clinical manifestations over time were observed, and the cohort characteristics were similar to international reports, confirming its representativeness for the GCA-affected population.
- An analysis of historical cohort data of GCA patients followed at ASST Spedali Civili di Brescia aiming to identify prognostic factors of severity, focusing on large vessel involvement, development of blindness, and hospitalization. Risk factors for large vessel involvement included younger age at diagnosis and the presence of systemic symptoms, while risk factors for blindness were older age and more comorbidities at diagnosis, particularly hypertension and chronic kidney disease.

The patients at higher risk for hospitalization included smokers, those with hypertension, chronic kidney disease, and comorbid conditions. Most hospitalizations were due to infections or cardiovascular complications, suggesting a possible correlation with the side effects of steroidal and immunosuppressive therapies.

- An analysis of the current state of therapy for GCA, focusing on GC- side effects and steroid-sparing effect of TCZ. Approximately 90% of patients developed at least one side effect, with GC-induced damage correlated with the cumulative GC dose and the presence of comorbidities at diagnosis. The use of TCZ reduced the cumulative GC dose by 25%, decreasing associated damage and the risk of disease relapse.
- A study on the identification of new biomarkers, analyzing the potential role of lymphocyte subpopulations (Th17 and Treg), which may be implicated in the disease's pathogenesis. Th17 cells, which are pro-inflammatory, decreased post-treatment, especially in responder patients transitioning from an active to an inactive disease state. No significant changes in Treg cells were observed, although a slight trend towards reduction was noted.

Lastly, Section 2 of the thesis includes research projects dedicated to other systemic vasculitides, such as Eosinophilic Granulomatosis with Polyangiitis (EGPA) and ANCA-associated vasculitides (AAV).

SECTION 1:

DEVELOPMENT OF NEW PERSONALIZED DIAGNOSTIC AND THERAPEUTIC STRATEGIES IN GIANT CELL ARTERITIS:

IDENTIFICATION OF NEW MARKERS FOR DISEASE SUBSETS AND PREDICTORS OF THERAPEUTIC RESPONSE

1.1 BACKGROUND

1.1.1 DEFINITION

Giant cell arteritis (GCA) is a systemic vasculitis that affects large-caliber vessels, such as the aorta and epiaortic vessels, with a particular preference for the arterial branches of the carotid and vertebral arteries. The frequent and typical involvement of the temporal artery led to the term "temporal arteritis," which was historically used to refer to this condition. However, this nomenclature is now considered outdated, as the disease affects more than just the superficial temporal artery. It is also historically known as Horton's arteritis, named after Dr. Arthur Columbus Horton, who first described its clinical features in 1932 [1].

1.1.2 EPIDEMIOLOGY

GCA is a rare disease with a global prevalence of less than 0.05% and an incidence ranging from 4 to 20 cases per 100,000 inhabitants. There are few epidemiological studies on the disease in the literature, predominantly conducted in Northern European countries and the United States, particularly in Olmsted County, Minnesota. To date, the only epidemiological studies on GCA in Italy have been carried out in the geographically limited area of the province of Reggio Emilia. The cited studies have not demonstrated complete concordance, revealing differences in the analyzed cohorts based on geographic territory.

In Scandinavian countries, the incidence of GCA is significantly higher. Iceland appears to have the highest number of diagnoses, with a biopsy-proven incidence of 43.6 cases per 100,000 inhabitants reported in a recent prospective study conducted over a 39-year period [2]. Similarly, in Sweden, another study recorded an incidence of 14.1 cases per 100,000, again using temporal artery biopsy (TAB) as a diagnostic criterion [3]. In Olmsted County, Minnesota, the incidence is comparable to that of Scandinavian countries, as the residents have Northern European ancestry [4]. Populations belonging to the same ethnic background exhibit similar risks; it is likely that unidentified genetic and possibly environmental factors significantly influence the risk of GCA across different populations. In contrast, the incidence of GCA is much lower in Japan (1.5 cases per 100,000) [5]

and Turkey (1.1 cases per 100,000) [6], while data and studies on African, South American, and continental Asian countries are lacking.

In Italy, the two main epidemiological studies on GCA focused on the province of Reggio Emilia, which will be referenced for Italian data, as it is the only area studied sufficiently to represent the national epidemiological reality of GCA, albeit within a limited scope.

The first study is a retrospective cohort study that identified patients diagnosed with GCA via temporal artery biopsy over a 26-year period, from 1988 to 2012. The biopsy-proven incidence of GCA in individuals over 50 years of age was found to be 5.8 cases per 100,000, increasing to 7.4 cases per 100,000 when considering only women aged over 50. In men over 50, the incidence was 3.3 cases per 100,000, representing a reduction of more than half. The prevalence in 2012 for the entire population was 30.4 cases per 100,000, with a significantly higher prevalence in women (45.3 cases per 100,000) compared to men (14.9 cases per 100,000). When focusing on individuals older than 50 years, the prevalence rose to 87.9 cases per 100,000, confirming a higher incidence in females and among the elderly population [7].

To investigate the full spectrum of clinical forms of GCA, another epidemiological study was recently conducted in the province of Reggio Emilia, utilizing different inclusion criteria. This study not only considered patients with the cranial phenotype of GCA and thus positive TAB but also subjects with large vessel GCA (LV-GCA) phenotypes without temporal artery involvement, where the TAB is negative, necessitating imaging of large vessels for diagnosis. The incidence of GCA in the population above 50 years was found to be 8.3 cases per 100,000, which is greater than previously reported, with an overall incidence in line with other Southern European countries. This study of both phenotypes allowed for the observation of epidemiological differences between cranial GCA and large vessel GCA. Notably, the majority of patients (60%) presented with cranial GCA, 25% had exclusive involvement of large vessels (LV-GCA), and 15% exhibited both positive TAB and manifestations of large vessel involvement. The annual incidence of cranial GCA was observed to be double that of LV-GCA, with the incidence in females consistently greater—approximately double—across both phenotypes.

Regarding the incidence of the two different phenotypes across various age groups, the annual incidence rate of cranial GCA peaked among those aged 80 to 89 years, whereas LV-GCA showed a more premature peak, with a fivefold increase observed between the 50-59 and 60-69 age groups, stabilizing thereafter. The prevalence reported in the province of Reggio Emilia as of December 2016 was 41.9 cases per 100,000 for the total population, and 101.3 cases per 100,000 when considering only individuals over 50 years of age [8].

1.1.3 PATHOGENESIS

From a pathogenic perspective, GCA is considered a multifactorial disease, where age, sex, genetic predisposition, and environmental factors play a predominant role. Genome-wide association studies (GWAS) have shown a strong association between GCA and certain gene variants within the major histocompatibility complex (MHC), particularly the HLA (Human Leukocyte Antigen)-DRB104:04, HLA-DQA103:01, and HLA-DQB1*03:02 variants. The amino acids encoded by these genes are located in the binding pocket of the MHC molecule, confirming the role of adaptive immunity and the potential antigen-mediated pathogenesis of GCA [9]. Other studies have demonstrated a possible role for non-HLA gene variants related to genes involved in angiogenesis and vascular remodeling mechanisms, such as PLG and P4HA2, and genes regulating CD4+ helper T (Th) cells and regulatory T cells (Treg), particularly the PTPN22 gene [10]. Specific environmental triggers directly involved in the pathogenesis of GCA have not yet been identified, although some epidemiological studies have noted a periodic increase in GCA incidence with six-year peaks, correlating it with viral outbreaks [11]. In addition, studies conducted on superficial temporal artery biopsies have identified various viral sequences, particularly from the varicella-zoster virus (VZV), but no sufficiently strong causal link has been demonstrated to support its pathogenic role [12].

Immunopathological and histopathological studies have shown the presence of an inflammatory infiltrate in the arterial wall, predominantly composed of CD4+ Th cells and macrophages, which subsequently differentiate into multinucleated giant cells, leading to the formation of non-caseating granulomas [13]. Local vascular

inflammation appears to be initiated by the activation of dendritic cells (DC) located in the adventitia of arteries, in response to an unknown antigen. Once activated, DCs process and present the antigen, expressing MHC class II and costimulatory molecules, such as CD83 and CD86, which are required for the activation and differentiation of two specific Th cell subpopulations. On one hand, IL (Interleukin)-12 and IL-18 production stimulates the differentiation of Th1 cells and the production of IFN (Interferon)-γ, which is markedly expressed in the walls of arteries affected by GCA and plays a crucial role in macrophage activation and granuloma formation [14]. On the other hand, the production of IL-1β, IL-6, IL-12, IL-22, and IL-23 stimulates the differentiation and survival of Th17 cells, which produce IL-17A, an interleukin with pleiotropic effects on various cell types, including macrophages, endothelial cells, vascular smooth muscle cells (VSMCs), and fibroblasts. Treg cells are also present in vascular lesions, but it has been hypothesized that, under the influence of IL-6, these cells may lack suppressive activity and instead produce IL-17A, contributing to the pathogenesis of GCA [15]. B lymphocytes have also been detected within the inflammatory infiltrate, appearing to contribute to T cell activation and potentially forming tertiary lymphoid organs, though the significance of this finding is not yet fully understood [16]. CD16+ non-classical macrophages are primarily responsible for vascular damage, producing various pro-inflammatory cytokines with both local and systemic effects. The expression of IL-1β, TNF (Tumor Necrosis Factor)-α, IL-33, IL-6, and various chemokines promotes the differentiation of VSMCs into a pro-inflammatory phenotype and induces the expression of endothelial adhesion molecules, which are necessary for the recruitment of additional lymphocytes and monocytes. In particular, IL-6 expression has been demonstrated in temporal artery biopsies from GCA patients, and a correlation between IL-6 levels and disease activity has been observed [17,18]. Simultaneous synthesis of VEGF (Vascular Endothelial Growth Factor), bFGF (basic Fibroblast Growth Factor), and PDGF (Platelet-Derived Growth Factor) by macrophages and multinucleated giant cells induces neovascularization, or the formation of new vasa vasorum within the arterial wall, facilitating the further recruitment of circulating leukocytes and meeting the metabolic demands needed to sustain the inflammatory process [19].

Vascular damage leads to the loss of VSMCs in the media layer, which may be due to oxidative damage from ROS (Reactive Oxygen Species) produced by macrophages and VSMC apoptosis induced by cytotoxic CD8+ T cells, which are often present in the inflammatory infiltrate [20,21]. Additionally, an imbalance between proteolytic and anti-proteolytic functions is observed. Increased synthesis of matrix metalloproteinases, MMP9 and MMP2, with elastinolytic activity, and reduced synthesis of their inhibitors, TIMP1 and TIMP2, result in the destruction of the arterial internal elastic lamina, potentially explaining the occurrence of some GCA complications, particularly aortic aneurysms [22]. Vascular damage leads to vascular remodeling, characterized by intimal hyperplasia and occlusion of the vascular lumen, underlying the ischemic complications of GCA. Specifically, macrophages and damaged VSMCs produce various growth factors and cytokines that promote the myofibroblastic differentiation of VSMCs and their migration to the intima. Myofibroblasts subsequently synthesize extracellular matrix proteins, such as fibronectin, collagen I, collagen III, and angiogenin, contributing to vascular remodeling. Among the factors implicated in this process are PDGF, FGF (Fibroblast Growth Factor)-2, TGF (Transforming Growth Factor)-β, EGF (Epidermal Growth Factor), endothelin-1, and several neurotrophic factors. In vitro studies on cell cultures derived from superficial temporal artery biopsies from GCA patients have shown that PDGF is the main factor contributing to the proliferation and migration of the human temporal artery-derived myointimal cell (HTAMC) population [23].

1.1.4 CLINICAL MANIFESTATIONS

The clinical onset of GCA tends to be subacute or acute, often preceded by nonspecific constitutional symptoms. Subsequently, inflammation of the vascular wall and tissue ischemia lead to the typical symptoms of the disease, which are specific to the affected vascular region. The average latency period between clinical onset and diagnosis is approximately 7 months, although it can range from 1 to 48 months [24].

1.1.4.1 CONSTITUTIONAL SYMPTOMS

Constitutional symptoms associated with GCA are common at the onset and include fever, weight loss, anorexia, musculoskeletal pain, and general malaise. Fever is observed in more than 25% of cases and may even be the only presenting symptom [24]. A Belgian study estimated that one in six cases of fever of unknown origin (FUO) in individuals aged 65 or older is due to GCA [25].

1.1.4.2 POLYMYALGIA RHEUMATICA

In 40-60% of patients, GCA is associated with polymyalgia rheumatica (PMR). This condition is characterized by symmetrical proximal polyarthralgia, myalgia, and morning stiffness. Pain symptoms mainly affect the pelvic girdle, shoulder girdle, and posterior cervical region. Morning stiffness typically lasts for several hours, and in some cases, it can persist throughout the day. Occasionally, stiffness may arise even after a short period of physical inactivity (the "gelling" phenomenon). Shoulder girdle symptoms are often due to subdeltoid/subacromial bursitis, biceps tenosynovitis, or less frequently, glenohumeral synovitis. Pelvic girdle symptoms, on the other hand, are secondary to hip bursitis or tenosynovitis involving the tendons of the gluteal or leg muscles. Rarely, PMR may be associated with RS3PE syndrome (Remittent Seronegative Symmetrical Synovitis with Pitting Edema), characterized by symmetric, seronegative, distal synovitis, predominantly affecting the hands [26].

1.1.4.3 CRANIAL SYMPTOMS

Headache is the most common symptom reported by patients at clinical onset. Classically, it presents as a new-onset unilateral throbbing headache in the temporal region, indicating involvement of the superficial temporal artery, but it may also extend to the frontal and/or occipital regions and can be bilateral. It does not exhibit the typical characteristics of other types of headaches (such as tension-type, cluster, or migraine) and is generally unresponsive to standard headache medications. Additionally, it tends to progressively worsen over time and is often associated with scalp hyperalgesia [27].

Masseter claudication occurs in approximately 50% of cases and is caused by involvement of the internal maxillary artery or one of its branches. It is characterized by cramp-like pain and mandibular fatigue that arise during chewing and subside with rest. In some cases, masseter claudication can lead to trismus and limitation of temporomandibular joint movement, either real or perceived [28].
In less than 10% of cases, lingual claudication can occur, characterized by glossodynia and macroglossia [29]. An even smaller percentage of cases may present with pharyngeal claudication, marked by dysphagia due to the involvement of the ascending pharyngeal artery. Scalp necrosis and lingual infarction are now rare, but they were previously reported in patients with long-standing, untreated GCA with bilateral involvement of the lingual arteries or arteries supplying the scalp [30][31].

1.1.4.4 OCULAR MANIFESTATIONS

Ocular symptoms are present in more than one-third of GCA patients and are caused by ischemic damage to the optic nerve, due to involvement of one or more branches of the ophthalmic artery. In most cases, ocular symptoms begin with transient vision loss (amaurosis fugax), which can be monocular or binocular. Patients may also experience peripheral visual field narrowing or blurred vision. If these symptoms are not recognized and promptly treated, progressive arterial occlusion leads to irreversible ischemic damage, resulting in permanent vision loss, which can be partial or complete, and either monocular or binocular. This condition affects 15-20% of patients.
Several risk factors have been studied to stratify the risk of blindness, including hypertension, thrombocytosis, masseter claudication, and age. However, the only factor proven to be predictive is amaurosis fugax [32]. Additionally, elevated serum levels of acute-phase proteins, particularly C-reactive protein (CRP), correlate with a higher risk of visual symptom progression [33]. Prompt steroid therapy reduces the risk of developing visual symptoms and their progression to irreversible blindness or involvement of the contralateral eye in patients with initial monocular involvement [34].

In about 85% of cases, the cause of permanent vision loss is arteritic anterior ischemic optic neuropathy (A-AION), due to involvement of the short posterior ciliary arteries, which are the branches of the ophthalmic artery primarily responsible for vascularizing the optic nerve. Less common is arteritic posterior ischemic optic neuropathy (A-PION), resulting from involvement of branches of the pial arteries, which supply the retrobulbar portion of the optic nerve. Another infrequent cause is central retinal artery occlusion (CRAO), and even rarer is branch retinal artery occlusion (BRAO). A relatively rare cause of blindness is cerebral ischemia of the occipital lobe due to vertebrobasilar insufficiency. This typically presents with homonymous hemianopsia, but in even rarer cases, occipital infarction can extend bilaterally, causing cortical blindness.

Ocular motility disorders occur in approximately 5% of GCA cases and are mainly due to the involvement of the muscular branches of the ophthalmic artery. They can also result from ischemia of the oculomotor nerve, trochlear nerve, abducens nerve, or one or more motor nuclei of these cranial nerves, which are located in the pons and midbrain. Diplopia, often transient, is the most frequent symptom and has high specificity for GCA when considered in this clinical context [35].

Charles Bonnet syndrome is a condition associated with vision loss, characterized by the occurrence of complex visual hallucinations in patients without psychiatric disorders. It is rare in GCA [36].

1.1.4.5 NEUROLOGICAL MANIFESTATIONS

Involvement of the central nervous system (CNS) in GCA is rare and the most common manifestation is ischemic stroke.

The main characteristic of ischemic stroke due to GCA is involvement of the vertebrobasilar system, which is observed in more than 50% of cases and is highly suggestive of GCA, especially when it occurs bilaterally. Common symptoms include vertigo, ataxia, dysarthria, homolateral hemianopia, or cortical blindness [37]. In contrast, ischemic stroke due to vertebrobasilar insufficiency is five times less frequent than stroke caused by internal carotid insufficiency in the general population [38].

1.1.4.6 LARGE VESSEL GCA

In about two-thirds of patients with GCA, the disease also affects the aorta and larger arteries. This subset is termed "large vessel GCA" (LV-GCA), which can manifest with or without cranial involvement. There are notable differences between the clinical and diagnostic profiles of cranial GCA (C-GCA) and LV-GCA. One major difference is the age of onset: patients with LV-GCA tend to be younger than those with cranial involvement. A study of 240 patients with radiographic evidence of LV-GCA found an average onset age of 68 years for LV-GCA compared to 76 years for C-GCA.

Another significant difference is the clinical presentation. While cranial symptoms like headache, jaw claudication, or vision loss are absent in LV-GCA, constitutional symptoms such as fever and weight loss are more frequent and may be the sole manifestation of the disease. This lack of typical cranial symptoms often leads to a delayed diagnosis, with a median latency of 3.5 months compared to 2.2 months for C-GCA [9].

Among large vessels, the subclavian arteries are most frequently affected in LV-GCA, with a typical bilateral involvement. This manifests clinically as intermittent claudication of the upper limbs, arterial bruits, and reduced distal blood pressure. Iliac and lower limb arteries are less commonly involved. Although subclavian artery involvement leads to progressive stenosis, complete vascular occlusion is rare.

Visceral and coronary artery involvement is infrequent but associated with a poor prognosis. Coronary arteritis occurs in less than 2% of GCA cases and is often identified post-mortem following a fatal acute myocardial infarction (AMI). Patients with GCA and acute coronary syndrome (ACS) also face a high rate of restenosis (36-78%) [39].

Non-productive cough is a relatively common symptom in GCA, though its cause is unclear. It may be linked to involvement of the pharyngeal, bronchial, or ascending pharyngeal arteries. Mesenteric artery involvement can present with postprandial abdominal pain (abdominal claudication), though progression to intestinal infarction is rare but serious [40].

The subclinical progression of large vessel involvement increases the risk of complications, such as aortic aneurysms, dissections, and valvular disease. Aortic aneurysms occur in 10-20% of patients, often developing 5 to 10 years after the initial diagnosis of LV-GCA. Thoracic aortic aneurysms are more common than abdominal aortic aneurysms, with a 17-fold increased risk for thoracic aneurysms compared to a 2.4-fold increase for abdominal aneurysms. Aortic dissections and ruptures, occurring primarily in the thoracic aorta, are seen in 1-6% of patients [41–44].

1.1.5 DIAGNOSIS

The diagnosis of GCA should be considered in individuals over the age of 50 who present with or have experienced one or more of the following symptoms or signs: new-onset headache, visual disturbances, jaw claudication, upper limb claudication, fever of unknown origin (FUO), anemia, or other constitutional symptoms and signs, along with elevated inflammatory markers. Additionally, a current or previous diagnosis of polymyalgia rheumatica (PMR) significantly raises the suspicion of GCA, especially when associated with any of the aforementioned indicators. Patients diagnosed with PMR should therefore be closely monitored and informed about the potential development of GCA symptoms during follow-up.

1.1.5.1 OPHTHALMOLOGICAL EXAMINATION

The fundoscopic examination (fundus exam) is recommended for patients with subjective visual acuity alterations. In patients with amaurosis fugax, the exam may appear normal or may show cotton-wool spots on the retina, indicative of localized retinal ischemia. In patients with arteritic anterior ischemic optic neuropathy (A-AION), the examination reveals papilledema and a waxy pallor of the optic nerve head, typically as a late finding.

For patients with arteritic posterior ischemic optic neuropathy (A-PION), the fundoscopic exam may not reveal signs of optic nerve involvement, as the retrobulbar portion of the nerve is affected. In such cases, examining pupillary reflex changes can help assess unilateral optic nerve involvement.

In patients with central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO), the fundoscopic exam may show retinal microhemorrhages (cherry-red spot) or stenotic or occluded retinal vessels. Diplopia is usually transient but, if present, may be associated with reduced extraocular movements. In cases of diplopia due to brainstem ischemic stroke, the exam might reveal skew deviation, a vertical misalignment not attributable to ocular palsy, and the patient may present with monocular or binocular blindness [45].

1.1.5.2 LABORATORY TESTING

GCA is characterized by systemic inflammation, which can be demonstrated through blood tests. Specifically, the complete blood count (CBC) may show the presence of normochromic and normocytic anemia, typically mild to moderate in severity, along with reactive thrombocytosis, while the white blood cell count is often normal or only slightly elevated, even in patients with systemic inflammation. Inflammatory markers, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are frequently elevated. Although not specific biomarkers, these are commonly used in clinical practice to help guide the diagnosis of GCA, though normal values should not exclude a possible diagnosis. Additionally, ESR and CRP are monitored during follow-up to assess the risk of disease relapse. About 30% of patients show elevated serum concentrations of liver enzymes, particularly alkaline phosphatase, while albumin levels may be moderately reduced. These parameters tend to normalize quickly with glucocorticoid treatment [46].

1.1.5.3 HISTOPATHOLOGIC FINDINGS

The current gold standard for diagnosing GCA is a temporal artery biopsy (TAB) [47]. However, the waiting period for conducting a TAB and receiving histological results should not delay the initiation of glucocorticoid therapy, which should be started promptly to prevent ocular complications, despite the treatment reducing the sensitivity of the TAB. A study on 78 subjects with suspected GCA who underwent TAB during treatment at different time intervals revealed that the rates of patients with a positive TAB at less than 2 weeks, less than 4 weeks, and more than 4 weeks

were 78%, 65%, and 40%, respectively. In some patients, TAB can still be diagnostic even weeks or months after starting steroid therapy [48].

The biopsy procedure involves removing a segment of the superficial temporal artery. The extracted segment should be at least 1–2 cm long because GCA affects the arterial walls in a segmental manner, and a shorter segment could miss the lesions (skip areas), leading to a false negative result.

Histological analysis of the sample typically shows granulomatous panarteritis (TMI, Trans-Mural Inflammation), often more pronounced in the tunica media and composed of CD4+ Th lymphocytes, macrophages, and multinucleated giant cells, which are quite common. However, their absence should not preclude a diagnosis. The internal elastic lamina is often fragmented, sometimes even in the absence of an inflammatory infiltrate; the significance of this finding is uncertain but should not be considered a marker of disease activity [49]. On the other hand, fibrinoid necrosis is never present in GCA; its presence may suggest necrotizing vasculitis.

In addition to this classic pattern, three other inflammatory patterns associated with GCA have been described: small vessel vasculitis (SVV), limited to the vessels in the peri-adventitial connective tissue; vasa vasorum vasculitis (VVV), limited to the adventitial vasa vasorum; and a pattern with inflammation limited to the adventitia (ILA), where inflammation extends from the perivascular area to the surrounding adventitia without involving the tunica media. A study conducted on 888 TABs from 871 patients between 1986 and 2013 showed that of the 354 (39.9%) positive biopsies, 274 cases (77.5%) were TMI, 32 cases (9%) were SVV, 25 cases (7%) were ILA, and 23 cases (6.5%) were VVV [50]. In these patterns, granulomas and multinucleated giant cells are rarely present, with lymphocytes and macrophages predominating.

TAB is highly specific but has variable sensitivity, influenced by the length of the biopsy segment. Sensitivity is highest with biopsy segments of 1.5–2 cm, while shorter segments increase the risk of false negatives [51]. A systematic review found a sensitivity of 86.9%, and a meta-analysis identified jaw claudication and diplopia as the symptoms most strongly associated with a positive biopsy, with likelihood ratios of 4.2 and 3.4, respectively [52].

1.1.5.4 IMAGING

Color Doppler Ultrasound (CDUS) has been proposed as a non-invasive alternative to biopsy for diagnosing GCA. While it has clear advantages, such as being non-invasive and low-cost, it exhibits lower sensitivity and specificity and is operator-dependent [53] (Dejaco, et al., 2018).

In C-GCA, the superficial temporal artery shows the "halo sign" on CDUS, indicating wall edema. The OMERACT group defined this sign as a homogeneous, hypoechoic, and well-demarcated thickening of 0.3-2 mm of the arterial wall. Additionally, when compressing the arterial lumen with the ultrasound probe, the halo sign persists, known as the "compression sign," which is also specific for C-GCA. Other detectable signs include stenosis and occlusions, but these do not significantly improve diagnostic sensitivity or specificity. CDUS offers multiple benefits: low cost, non-invasiveness, no exposure to ionizing radiation, and the provision of both structural and functional information about the analyzed vessel. However, its primary limitation lies in variable sensitivity and specificity across studies. For example, a meta-analysis of 285 patients evaluated with both CDUS and temporal artery biopsy (TAB) estimated a sensitivity of 68% and specificity of 91%. A systematic review of ten studies involving 696 patients reported a sensitivity range of 55-100% and specificity of 78-100%. This variability may stem from the operator-dependent nature of CDUS, the type of technical equipment, and the clinical context [54] [55]. Furthermore, the halo sign tends to disappear within 2-4 weeks after starting steroid therapy, so CDUS should ideally be performed as soon as possible, preferably within one week of initiating treatment, without delaying the therapy.

Based on this, the EULAR (European League Against Rheumatism) guidelines recommend using CDUS of the temporal and axillary arteries as the first diagnostic investigation to confirm suspected C-GCA [53].

In diagnosing suspected GCA, early identification of large vessel involvement is essential, but no validated markers currently exist to assess the risk of severe aortic involvement. Imaging techniques, including CDUS, 18FDG-PET, MRI, MRA, and CT, are crucial for diagnosing large vessel GCA, each with unique advantages and limitations. The 2021 ACR/VF guidelines recommend imaging studies for patients

with a new diagnosis of GCA to evaluate potential large vessel involvement. However, many questions remain regarding the choice of imaging modality and timing [47].

CDUS is used to study axillary arteries and allowed to identify increased intimal-medial thickness (IMT), with cut-off values of 1 mm, but can't evaluate thoracic arteries. CTA identifies luminal alterations, wall thickening, and the "double ring enhancement" sign can be observed. CTA has higher spatial resolution and shorter execution time compared to MRA, but exposes patients to high doses of ionizing radiation. A single study on CTA in diagnosing LV-GCA reported a sensitivity of 73% and specificity of 78% [56] [57]. The 18FDG-PET shown sensitivity and specificity rates of 67-77% and 66-100%, respectively. Limitations include low availability, high costs, and significant radiation exposure, though it can help exclude concurrent diseases, particularly neoplastic ones. Whole-body scintigraphy using hybrid machines (18FDG-PET/CT) significantly improves diagnostic accuracy.

For MRI, MRA is recommended, preferably with a 3T scanner, evaluating the aorta and major branches from the carotid bifurcation to the iliac bifurcation, including axillary and brachial arteries. Sequences like black-blood, STIR, and T1-weighted should be acquired pre- and post-contrast to assess arterial narrowing, dilation, thickening, and increased contrast uptake, which may indicate active inflammation, although its role in monitoring recurrences is unproven [53].

In conclusion, following EULAR recommendations, imaging is vital for diagnosing LV-GCA. EULAR guidelines suggest using 18FDG-PET and CT as first-line diagnostic investigations, reserving other imaging techniques for uncertain cases. Furthermore, traditional angiography should be excluded from the diagnostic process due to invasiveness and inability to adequately visualize arterial walls [53].

1.1.5.5 CLASSIFICATION CRITERIA OF GCA

The classification criteria for GCA are not intended for establishing a clinical diagnosis. In 1990, the American College of Rheumatology (ACR) established classification criteria for major forms of vasculitis, including GCA. Five parameters were identified: age of onset ≥ 50 years, new localized headache, swelling and

thickening of the superficial temporal artery, erythrocyte sedimentation rate (ESR) ≥ 50 mm/h, and a temporal artery biopsy (TAB) suggestive of GCA. The presence of three or more of these criteria was sufficient to classify a patient as having GCA, with a sensitivity of 93.5% and specificity of 91.2% [58]. Originally developed to differentiate GCA from other forms of vasculitis in research contexts, these criteria do not possess sufficient sensitivity and specificity for diagnosing individual patients, expecially patients with Large Vessel involvement. However, they can still serve as a helpful reminder for clinicians regarding key factors relevant to making a GCA diagnosis.

These criteria were recently updated in 2022 by the ACR and the European Alliance of Associations for Rheumatology (EULAR). The updated criteria employ a weighted algorithm that incorporates clinical, laboratory, imaging, and biopsy factors. This new approach aims to better identify patients whose disease primarily affects the large vessels, such as the aorta and axillary arteries [59].

1.1.6 THERAPY

1.1.6.1 GLUCOCORTICOIDS

The treatment for GCA primarily involves the use of high-dose glucocorticoids (GCs), which should be initiated as early as possible to minimize the risk of acute complications, particularly ocular ones.

According to EULAR recommendations, in the absence of ocular manifestations, the recommended starting dose is 1 mg/kg/day of prednisone or an equivalent oral glucocorticoid, typically between 40-60 mg/day. If the patient exhibits ocular symptoms, it is advisable to start with intravenous boluses of methylprednisolone at doses of 250-1,000 mg/day for at least three days, followed by oral GCs at the previously mentioned dosages [60]. Once the disease is in remission—defined as the absence of clinical symptoms and normalization of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)—a gradual reduction in GC dosage can begin. EULAR guidelines suggest reducing the dose to 15-20 mg/day within 2-3 months, followed by a decrease to 5 mg/day or less after the first year. The optimal

duration of steroid therapy is not fully established, but most experts agree that it should not be discontinued before two years [60].

The tapering process should be closely monitored through clinical and laboratory follow-up, with dosage adjustments made only if the patient remains in sustained remission. However, approximately 40% of patients may experience vascular progression or disease relapse during this tapering phase. In large vessel GCA, relapses may also include the progression of aortic stenosis or dilation, or the occurrence of aortic dissection. In such cases, in addition to treating specific complications, it is necessary to reinstate high-dose GC therapy and/or consider immunosuppressive therapy.

1.1.6.2 TOCILIZUMAB

During the tapering of glucocorticoids (GCs), about 40% of patients may experience a relapse or progression of vascular disease. Moreover, chronic use of GCs is associated with over 80% incidence of side effects, including diabetes mellitus, hypertension, early atherosclerosis, cardiovascular diseases, infections, and osteoporosis. Consequently, there has been increasing interest in using immunosuppressive drugs as steroid-sparing agents in conjunction with GCs, although guidelines for their use are still being defined. The 2018 EULAR recommendations suggest that steroid-sparing drugs should be considered as an additional therapy for patients who develop relapses, have refractory disease, or experience complications from GCs, particularly those at high risk for GC-related side effects [60]. Conversely, the 2021 ACR guidelines recommend the use of an immunosuppressive agent, specifically Tocilizumab (TCZ), for all newly diagnosed GCA patients [47].

Both guidelines agree that TCZ should be the first-line steroid-sparing drug. This monoclonal antibody targeting the IL-6 receptor was approved by the FDA and EMA in 2017 for GCA treatment. The use of TCZ is supported by two significant randomized controlled trials (RCTs) showing that adjunctive therapy with TCZ can reduce the risk of relapse and cumulative GC dosage compared to steroid monotherapy [61] [62]. In total, 170 GCA patients were treated across these studies, both demonstrating TCZ's superiority over placebo in achieving and maintaining

disease remission after 52 weeks. However, long-term follow-up data reveal a 50% relapse rate after discontinuation of therapy [63,64]. Due to the rarity of GCA and TCZ's recent approval, literature provides limited studies on its use in real-life cohorts, although findings seem to confirm RCT results regarding both efficacy and relapse risk upon withdrawal [65,66]. Currently, there is insufficient data to establish the optimal duration of TCZ treatment or specific tapering regimens for GCs and TCZ. Therefore, international recommendations advocate for individualizing therapy based on patient's clinical history and characteristics [60].

1.1.6.3 OTHER IMMUNOSUPPRESSIVE DRUGS

Conventional immunosuppressive drugs (cDMARDs), including Methotrexate (MTX), have shown partial efficacy in GCA and are therefore considered second-line treatments. Notably, there are currently no randomized controlled trials (RCTs) evaluating MTX for GCA; its efficacy has only been assessed in observational studies, which have yielded inconsistent results. A recent meta-analysis highlighted that Tocilizumab (TCZ) significantly reduces the relapse rate and cumulative dose of glucocorticoids in GCA patients after 52 weeks, while no other studied agents—including MTX, cyclophosphamide, leflunomide, hydroxychloroquine, and dapsone—have demonstrated similar efficacy [67]. Additionally, an RCT involving Abatacept (ABA), a biological drug that inhibits lymphocyte costimulation, showed that ABA could induce remission in 48% of patients with relapsing GCA [68]. In contrast, tumor necrosis factor-alpha (TNF-α) inhibitors, such as Adalimumab and Infliximab, have not proven effective in the treatment of GCA.

1.1.7 GLUCOCORTICOIDS ADVERSE EFFECTS

The risks associated with long-term high-dose glucocorticoid (GC) therapy are significant. A study conducted on 120 GCA patients from 1950 to 1991 found that 86% experienced at least one adverse drug reaction (ADR) related to chronic steroid use. Subsequent studies have reported lower incidence rates, sometimes below 16%, likely due to the incorporation of steroid-sparing medications into modern treatment protocols. There is a clear correlation between the frequency and severity

of ADRs and both daily and cumulative doses of GCs. A 2017 case-control study revealed that high daily doses of prednisolone are linked to an increased risk of serious ADRs. Specifically, patients on doses exceeding 30 mg/day had an adjusted odds ratio (AOR) of 4.7 (95% CI: 2.8-7.8) for developing diabetes mellitus, 1.9 (95% CI: 1.2-2.9) for osteoporosis, 2.6 (95% CI: 1.6-4.3) for fractures, 3.5 (95% CI: 2.0-6.1) for glaucoma, 3.3 (95% CI: 2.2-5.3) for severe infections, and 2.1 (95% CI: 1.3-3.5) for mortality [69].

1.1.7.1 IMMUNOSUPPRESSIVE EFFECTS AND INFECTIONS

Systemic steroid therapy has an immunosuppressive effect that increases the risk of infections. A retrospective study involving over 138,000 patients, primarily with polymyalgia rheumatica and GCA, found an infection incidence of 160.7 per 1,000 person-years, with an increased risk among older patients. Bacterial infections were the most common, and the risk rose with cumulative doses exceeding 7,300 mg of steroids. Commonly reported infections included lower respiratory tract infections (27.3%), conjunctivitis (8.6%), and herpes zoster (7.4%). Among hospitalized patients, 26.7% experienced mortality within 30 days, with 8.7% dying within 7 days of admission. The leading causes of death were pneumonia (52.6%), complicated urinary tract infections leading to sepsis (3%), and peritonitis (2.2%) [70]. A prospective study involving 486 GCA patients reported similar findings. The incidence of infections was 11.1 per 100 person-years for GCA patients compared to 5.9 per 100 person-years for controls. Infections such as pneumonia and septic shock were frequently observed and represented a significant cause of mortality. The risk of infections and mortality was highest in the first year of treatment and increased with age and conditions like diabetes. A prednisone dosage exceeding 10 mg/day at the end of the first year was associated with a significantly higher mortality rate from infections [71].

1.1.7.2 CUTANEOUS AND MUSCULOSKELETAL SIDE EFFECTS

Another common adverse drug reaction (ADR) associated with glucocorticoids (GC) is the occurrence of cutaneous side effects, particularly skin atrophy,

characterized by thinning and increased fragility of the skin, which is often accompanied by the appearance of bruising. The high frequency of these effects is related to their manifestation even at low doses of chronic steroid therapy [72].

Osteoporosis is a significant side effect of systemic steroid therapy. Initially, GCs increase bone resorption by stimulating osteoclastogenesis. However, with prolonged use, there is a suppression of new bone formation due to reduced proliferation and differentiation of osteoblasts, as well as increased apoptosis of osteoblasts and osteocytes. A retrospective cohort study of over 12,000 patients with PMR and nearly 2,700 with GCA showed a 14% incidence of osteoporotic fractures, with hip and femur fractures being the most common. The overall fracture risk was 63% in PMR patients and 67% in GCA patients compared to controls, with a higher risk of vertebral and wrist fractures. Women aged 50-60 were particularly affected, and fracture risk correlated with the dosage and duration of steroid therapy, peaking in the first year but remaining significant beyond five years. However, only a small percentage of patients received bisphosphonate therapy for osteoporosis [73].

Other musculoskeletal ADRs, less frequent than osteoporosis, include avascular necrosis (osteonecrosis) and steroid-induced myopathy. Osteonecrosis is relatively rare and occurs only with very high and continuous doses of GC drugs. One study reported an incidence of avascular necrosis of 0.004 events per patient-year. Steroid myopathy is also a relatively infrequent event and manifests as symmetrical proximal muscle weakness in both upper and lower limbs [74].

1.1.7.3 METABOLIC AND CARDIOVASCULAR SIDE EFFECTS

Hyperglycemia is one of the primary dose-dependent side effects of systemic steroid therapy. GC drugs increase circulating glucose levels, particularly postprandially. Moreover, PMR and GCA patients experience chronic systemic inflammation, which contributes to insulin resistance, potentially contributing to the high incidence of DM in this population. A meta-analysis of 25 studies estimated a cumulative incidence of 6% for PMR patients and 13% for GCA patients, with expected incidence rates of 4.8% and 7% over follow-up periods of 4.4 years for PMR and 6.4 years for GCA, respectively [75].

Weight gain, particularly central obesity, is also frequent, with studies indicating up to 70% of patients experiencing weight gain on steroid therapy [76].

Chronic therapy with high doses of GC can predispose individuals to develop hypertension, although the underlying pathogenic mechanisms remain largely unknown. Some authors suggest that hypertension may result from fluid retention, which could explain the higher incidence of hypertension among individuals with underlying cardiovascular and renal diseases. A retrospective cohort study evaluating 71,642 patients with chronic inflammatory diseases, including inflammatory bowel diseases, rheumatoid arthritis, PMR, systemic lupus erythematosus, GCA, and other vasculitides reported hypertension in 34.8% of patients, with an incidence rate of 46.7 per 1,000 person-years. The risk of developing hypertension was higher during periods of steroid therapy and among patients with higher cumulative doses, particularly in those with PMR and GCA [77]. Cardiovascular diseases, including premature atherosclerosis and myocardial infarction, are common complications. Dyslipidemia and iatrogenic Cushing's syndrome, other common side effects of GCs, can contribute to the development of atherosclerotic disease. A cohort study involving 1,420 PMR patients, 177 GCA patients, and 261 patients with both conditions estimated a 50% incidence of hypertension and 18% of major cardiovascular events (MI and stroke) [78] and a retrospective cohort study of 785 GCA patients with a mean follow-up of 12 months demonstrated a dose-dependent increase in the risk of cerebrovascular events [79].

Another ADR related to GC use is cardiac arrhythmias, particularly atrial flutter and atrial fibrillation. A case-control study highlighted that the use of GC was much more common among 20,221 patients with atrial flutter or fibrillation compared to 202,130 controls (6.4% vs. 2.6%). Furthermore, GC use was significantly associated with an increased risk of atrial flutter or fibrillation (AOR = 1.9) [80].

Overall, both metabolic and cardiovascular side effects are significant concerns in patients receiving systemic steroid therapy, particularly in those with underlying conditions like GCA and PMR.

1.1.7.4 GASTROINTESTINAL SIDE EFFECTS

The most frequent adverse drug reactions (ADRs) associated with glucocorticoids (GCs) include chronic gastritis, peptic ulcers, and gastrointestinal bleeding. The risk of these ADRs increases marginally with GCs alone, with a relative risk (RR) between 1.1 and 1.5. However, when combined with non-steroidal anti-inflammatory drugs (NSAIDs), the risk can increase up to fourfold compared to individuals not taking either medication, and nearly double compared to those taking only NSAIDs [81]. A study involving 785 patients with GCA reported incidences of peptic ulcers and gastrointestinal bleeding at 6%, 6.6%, and 11.8% for patients taking daily doses of prednisone of 1-25 mg, 25.1-40 mg, and over 40 mg, respectively, indicating a dose-dependent relationship for gastrointestinal ADRs. Rare complications may include gastrointestinal perforation and hepatic steatosis [82].

1.1.7.5 OPHTHALMOLOGICAL SIDE EFFECTS

Among the ophthalmologic ADRs, the most severe are cataracts, glaucoma, and exophthalmos. Cataracts are often bilateral and develop slowly, more frequently in the posterior subcapsular region. In patients with GCA treated with chronic steroid therapy, cataract development is very common, likely due to the presence of other risk factors such as systemic inflammation, diabetes mellitus (DM), and advanced age. Open-angle glaucoma occurs less frequently than cataracts, primarily because it manifests at higher doses of glucocorticoids (GCs). A cohort study in GCA patients treated with GCs found an incidence of glaucoma of 0.022 events per patient-year, whereas the incidence of cataracts was 0.158 events per patient-year, making it one of the most commonly reported complications. Another observational study conducted on 5,011 GCA patients estimated a glaucoma incidence of 4.2%, with a higher risk of glaucoma onset during the first year of treatment [83]. Exophthalmos, along with eyelid and extraocular muscle edema, are very rare complications that occur at very high doses of GCs and are associated with Cushingoid features.

1.1.7.6 ENDOCRINE SIDE EFFECTS

Among the endocrine ADRs associated with glucocorticoids (GCs) are iatrogenic Cushing's syndrome, hirsutism, and suppression of the adrenal-pituitary axis. Cushingoid features, such as central obesity, dorsal hump, and moon face, are among the most common. Suppression of the hypothalamic-pituitary-adrenal axis is a possible outcome, especially with abrupt discontinuation or rapid tapering of steroid therapy. This condition is characterized by adrenal atrophy and a lack of corticosteroid production due to the suppression of corticotropin-releasing hormone (CRH) from the hypothalamus and adrenocorticotropic hormone (ACTH) from the anterior pituitary. The occurrence of this ADR depends on the duration and dose of GC therapy, with significant individual variability likely due to differences in GC metabolism rates. In patients with GCA, this ADR is relatively uncommon. However, a prospective study on 150 patients receiving chronic steroid therapy estimated that up to 49% did not respond to an ACTH stimulation test, indicating altered adrenal function. Of these, 53% continued to have altered adrenal function after 12 months, and 15% after 36 months. In 5% of cases, a definitive diagnosis of adrenal insufficiency was made [84].

1.1.7.7 NEUROPSYCHIATRIC SIDE EFFECTS

GCs are associated with various neuropsychiatric disorders, including emotional lability, manic and hypomanic episodes, major depression, psychosis, delirium, confusion, spatial and temporal disorientation, cognitive and memory deficits, insomnia, and akathisia. Most of these conditions are moderate in severity and generally reversible after stopping the therapy, except for akathisia, which may persist. These side effects are more common in older individuals or those with a history of neuropsychiatric disorders [85]. Steroid-induced psychosis is the only condition proven to be dose-dependent, typically occurring with prednisone doses of 20 mg/day or higher administered over prolonged periods. About 10% of cases become persistent, requiring antipsychotic treatment [86]. Despite this, the overall frequency of neuropsychiatric disorders in patients with GCA is low. A cohort study of 8,777 GCA patients estimated an odds ratio (OR) of 1.04-1.05 for

neuropsychiatric disorders and 0.98-1.06 for depression [87]. However, insomnia appears to be more common, with an incidence of 30% in GCA patients [72].

1.1.8 FOLLOW-UP

1.1.8.1 CLINICAL AND LABORATORY FOLLOW-UP

The EULAR guidelines recommend follow-up visits every 1-3 months during the first year after a GCA diagnosis, and then at intervals of 3-6 months. For patients in sustained remission, annual follow-up is suggested. Each follow-up visit should include clinical and laboratory monitoring. Routine lab tests should include complete blood count (CBC) with leukocyte formula, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum protein electrophoresis, lipid profile, blood glucose, HbA1c, and liver and kidney function tests [60]. A rise in ESR and CRP typically signals disease relapse, though in a cohort study of 128 GCA patients, 21% of those who relapsed had normal ESR and CRP levels [88]. It's also important to note that tocilizumab (TCZ) suppresses CRP production, so CRP and ESR may remain normal in patients treated with TCZ. In the GiACTA trial, disease activity and relapses were assessed without considering CRP levels [61]. Other potential relapse markers being investigated include osteopontin, plasma calprotectin (S100A8/A9), and pentraxin 3 (PTX3), which are partly independent of the IL-6 pathway. PTX3 levels tend to rise in cases of recent optic nerve ischemia. Serum IL-6 levels also correlate with disease activity and appear to be a better marker of relapse than ESR levels. However, none of these markers have been fully integrated into clinical practice. Therefore, monitoring is still primarily based on inflammatory markers and clinical data. Clinical follow-up should include the evaluation of new or worsening symptoms, with particular attention to eye and cardiovascular examinations. Monitoring should also focus on detecting complications from pharmacological therapy [60].

1.1.8.2 IMAGING FOLLOW-UP

For long-term monitoring of vascular complications in large-vessel GCA (LV-GCA), imaging techniques like MRA (Magnetic Resonance Angiography), CTA

(Computed Tomography Angiography), and CDUS (Color Doppler Ultrasound) are recommended. The frequency and type of screening should be determined on an individual basis. The choice of imaging method depends on the number and type of arteries affected and patient-specific factors, such as allergies to contrast agents (MdC). For larger vessels like the aorta, MRA or CTA is preferred, while for smaller arteries like the subclavian, axillary, and brachial arteries, CDUS may be sufficient. Imaging follow-ups should be conducted both in patients in clinical remission to monitor for complications such as aneurysms, dissections, and stenosis, and in those suspected of disease relapse [53].

MRA is considered the best modality for monitoring disease activity in LV-GCA patients undergoing treatment. It can identify both luminal changes and disease activity by assessing wall thickness indicative of mural edema. Additionally, alternative contrast agents like gadofosveset, which is better at distinguishing between active and chronic vasculitis, have been proposed [56].

The role of 18FDG-PET/CT in diagnosing LV-GCA is well established, but its use in follow-up remains under debate. Up to 55% of patients in clinical and/or laboratory remission still show residual arterial 18FDG uptake. The interpretation of this residual uptake is still under investigation. One hypothesis suggests that residual 18FDG uptake reflects vascular remodeling, as vascular smooth muscle cells (VSMC) and myofibroblasts can also absorb the tracer. Another hypothesis suggests that it could indicate subclinical inflammation [56].

1.1.9 PROGNOSIS

GCA exhibits a variable course and duration. In some patients, the disease may regress within 1-2 years, allowing for the discontinuation of steroid therapy, while in others, it follows a chronic or relapsing course. GCA does not appear to significantly impact overall quality of life (QoL). A case-control study that assessed QoL using the SF-36 questionnaire found that up to 57% of patients experienced a significant improvement during treatment. Moreover, those with complications from GCA or steroid therapy did not show significant QoL differences compared to those without complications. Visual impairments and mobility difficulties were noted as major symptoms [89]. A recent analysis based on the GiACTA trial also

demonstrated improved health-related QoL (HR-QoL) in patients treated with TCZ and prednisone compared to those receiving a placebo and prednisone, further indicating that TCZ enhances QoL in GCA patients [90]. Regarding life expectancy, patients with cranial GCA (C-GCA) show no significant difference in survival compared to the general population. However, those with large-vessel GCA (LV-GCA) have a 2.4 times higher mortality risk than C-GCA, with a standardized mortality ratio of 2.63 (95% CI: 1.78-3.73). LV-GCA patients are more prone to frequent and earlier relapses and are often refractory to standard treatments [42][91].

The leading causes of death include infections, mainly respiratory infections, and cardiovascular events such as ischemic heart disease, aortic aneurysms, aortic dissections, and ischemic strokes, all of which significantly affect QoL. A case-control study conducted from 1972 to 2012, involving 2,577 controls and 881 GCA cases, estimated a hazard ratio (HR) of 2.34 (95% CI: 1.15-4.80) for infections and 1.31 (95% CI: 1.13-1.51) for cardiovascular events. At the end of the study, the average age at death was 83.5 years for GCA cases and 84.7 years for controls [92].

1.2 RATIONALE AND AIMS

GCA is a systemic vasculitis marked by inflammation of large-caliber arterial vessels. It typically presents with an acute or subacute onset, followed by a chronic course often associated with severe, irreversible, and debilitating complications. GCA is a rare condition, with an incidence ranging from 1 to 46 cases per 100,000 individuals over the age of 50.

The disease most commonly involves branches of the carotid artery, specifically affecting the superficial temporal artery, which leads to symptoms such as temporal headache, jaw claudication, and unilateral or bilateral blindness. In around two-thirds of cases, GCA also affects the aorta and other large vessels.

Due to its rarity and often insidious onset, GCA is challenging to diagnose early, which frequently results in diagnostic and therapeutic delays. These delays are associated with an increased risk of serious complications. Accurate diagnostic evaluation is essential to establish an effective treatment plan. The initial treatment of GCA involves high-dose glucocorticoids, but long-term use is linked with an incidence of side effects exceeding 80%, and approximately 40% of patients experience relapses during dose tapering. Given these concerns, there has been increasing focus on combining immunosuppressive drugs like Tocilizumab with glucocorticoids.

Despite significant advancements in the diagnosis and treatment of GCA, many questions remain about the optimal therapeutic approach for GCA patients. Based on the aforementioned challenges, the future of GCA treatment seems to lie in personalized medicine. Currently, there are no biomarkers available to identify clinical subsets of GCA or predict relapse risk and therapeutic response.

This thesis aims to expand the scientific understanding of GCA and lay the groundwork for future personalized approaches. The goal is twofold: to identify, based on specific biomarkers, each patient's risk of developing severe complications and to tailor treatments to prevent these; and to select the most effective therapy for each patient by identifying predictive response factors.

The thesis is structured into four main sections:

- An introductory study on the epidemiology of GCA in the ASST Spedali Civili di Brescia, offering a clinical and scientific snapshot of the context on which the following studies are based.
- A section focusing on the identification of prognostic factors for disease severity, divided into three chapters: analysis of risk factors for large-vessel involvement (a specific GCA subset), analysis of risk factors for blindness, and analysis of hospitalization and mortality risk in GCA patients.
- A third section detailing the state-of-the-art treatment for GCA, with a specific focus on risk factors for steroid-related side effects and prognostic factors for response to innovative therapies, including Tocilizumab.
- A final section exploring new potential biomarkers of disease, including an analysis of specific lymphocyte subpopulations that could serve as prognostic factors for disease severity and predictive markers for therapeutic response.

This thesis presents my scientific contributions through the results of various studies conducted over the last three years. My role in each study included active participation in research design and execution, as well as serving as a rheumatologist, writer, and statistician.

1.3 STUDY ON THE INCIDENCE OF GIANT CELL ARTERITIS IN ATS BRESCIA

1.3.1 AIM OF THE STUDY

GCA is a rare disease, with a global prevalence of less than 0.05% and an incidence of 4-20 cases per 100,000 inhabitants. In the literature, few epidemiological studies have been conducted on GCA, mainly in Northern European countries and the United States, particularly in Olmsted County, Minnesota [93]. To date, the only epidemiological studies on GCA in Italy have focused on a limited geographic area, namely the province of Reggio Emilia [7]. These studies have shown some discrepancies in the analyzed cohorts, likely due to geographic variations. Considering these gaps, a study was developed to examine the epidemiological reality of GCA in the ATS Brescia area, a region that had not been studied from this perspective before. The aim was to compare the findings with the few existing studies in the literature to provide a broader context for GCA incidence and characteristics.

The main objective of the study was to identify all patients diagnosed with GCA over a 6-year period in a well-defined area to calculate incidence and prevalence of the disease. Secondary aims of this study aims were to conduct the following analyses:

- Demographic characteristics: evaluate the demographic features of the patient cohort, focusing on age at diagnosis and gender distribution.
- Diagnostic process: Investigate how the diagnosis was made, assessing the diagnostic methods used (both laboratory tests and imaging), the diagnostic setting, and the time to diagnosis.
- Temporal changes: evaluate whether there were any significant changes in the number of patients, their clinical manifestations, and diagnostic approaches over the study period.
- Comparison with other epidemiological studies: conduct a comparative analysis with the findings from the few other existing epidemiological studies on GCA, with particular reference to the studies from the Reggio Emilia province.

1.3.2 METHODS

GCA is a rare disease, and according to the guidelines of the Italian National Plan for Rare Diseases (2013-2016), patients with rare disease need to be centralized in third-level centers (expertise centers). These centers have a significant volume of activity relative to the disease's prevalence, leading to higher experience and expertise. Expertise centers can provide not only accurate diagnoses but also appropriate follow-up and comprehensive patient care, adopting a multidisciplinary approach. They also serve as referral centers for second-level hospitals, forming a territorial network with close interaction between centers and centralizing the care of patients with rare diseases.

In the ATS Brescia area, the Spedali Civili of Brescia is the only third-level center, serving as the referral point for GCA diagnosis and follow-up for the entire ATS region. It is also the only center authorized to issue rare disease certificates and ticket exemptions for patients with GCA. Based on this framework, the identification of patients was carried out using two main databases and three secondary sources through the capture-recapture method. This method enhances the likelihood of identifying all cases within the population. The data sources were as follows:

- Database of patients diagnosed with GCA at the Rheumatology and Clinical Immunology Unit of Spedali Civili di Brescia, the only third-level center in the ATS Brescia region.
- Database of patients with rare disease certification for GCA registered with ATS Brescia.
- Databases of the second-level centers located within the ATS Brescia area:
    - ASST Franciacorta, Chiari Hospital
    - San Camillo Clinic, Cremona
    - ASST Spedali Civili, Montichiari Hospital

The study included patients residing within the ATS Brescia area who were diagnosed with GCA between January 1, 2016, and December 31, 2021. This comprehensive approach allowed for accurate identification and analysis of GCA

cases within the specified region and time frame, ensuring that the study captured a representative sample of the population affected by this rare disease.

1.3.3 RESULTS

A total of 141 patients were identified in the study. During the study period, an average of 24 new diagnoses of GCA were made per year. Specifically, 26 diagnoses were recorded in 2016, 21 in 2017, 20 in 2018, 33 in 2019, 22 in 2020, and 19 in 2021. This corresponds to an average incidence rate of 4.5 cases per 100,000 inhabitants aged over 50. Although some variability in the number of annual diagnoses was observed, the difference was not statistically significant.

Analysis of the entire cohort revealed that the majority presented with a cranial GCA (C-GCA) phenotype, with 92 patients (65.2%), while 27 patients (19.1%) had a large-vessel cranial GCA (LV-C GCA) phenotype, and 22 patients (15.6%) had large-vessel GCA (LV-GCA) without cranial involvement. There was a clear female predominance, with 97 patients (68.8%) being female, and 44 patients (31.2%) being male. The mean age at diagnosis was 74.1 years, with a median age of 74 years (interquartile range: 69-79 years).

The diagnostic delay, defined as the time from symptom onset to diagnosis, had a median of 4 weeks. The most common diagnostic setting for GCA was during hospitalization, which accounted for 99 cases (70.2%). This was followed by outpatient diagnoses in 36 cases (25.5%). Diagnoses made in the emergency department or observation unit (OBI) were less frequent, with 6 cases (4.3%).

Clinical and demographic data were categorized by the year of diagnosis to detect any changes over the study period in the clinical manifestations and their severity, as well as in the timing and methods of diagnosis. No significant variations were observed over time regarding clinical manifestations, sex distribution, or disease phenotype. Additionally, no significant differences were noted in the diagnostic setting, with hospital-based diagnoses consistently dominating throughout the entire period under review (Tables 1 and 2).

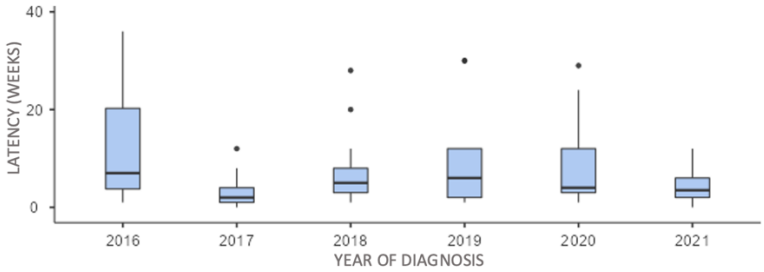
Clinical manifestations	2016	2017	2018	2019	2020	2021	p
Visual manifestations	4 (15,4%)	7 (33,3%)	6 (30,0%)	11 (33,3%)	9 (40,9%)	3 (15,8%)	0,8642
Headache	17 (65,4%)	18 (85,7%)	17 (85,0%)	27 (81,8%)	16 (72,7%)	13 (68,4%)	0,0710
Scalp tenderness	12 (46,2%)	14 (66,7%)	6 (30,0%)	17 (51,5%)	10 (45,5%)	8 (42,1%)	1,000
Jaw claudication	3 (11,5%)	5 (23,8%)	12 (60,0%)	11 (33,3%)	11 (50,0%)	7 (36,8%)	0,0698
Limbs claudication	3 (11,5%)	1 (4,8%)	0	1 (3,0%)	0	1 (5,3%)	0,6270
Stroke	0	1 (4,8%)	0	0	0	1 (5,3%)	0,4422
Fever	10 (38,5%)	6 (28,6%)	6 (30,0%)	10 (30,3%)	8 (40,0%)	8 (42,1%)	1,0000
Weight loss	15 (57,7%)	6 (28,6%)	7 (35,0%)	15 (45,5%)	11 (55,0%)	8 (42,1%)	0,3726
Fatigue	21 (80,8%)	13 (61,9%)	13 (65,0%)	24 (72,7%)	16 (80,0%)	16 (84,2%)	1,000
PMR	13 (50,0%)	11 (52,4%)	6 (30,0%)	16 (48,5%)	10 (50,0%)	8 (42,1%)	1,000

Table 1. Clinical manifestations at diagnosis. Data expressed as *n* (%)

Year	Diagnostic latency	Age at diagnosis	Diagnostic setting			Phenotipe		
			Outpatient	ER	Hospitalization	C	LV	LV-C
2016	7 (4-20)	73 (67-78)	6 (23,1%)	1 (3,8%)	19 (73,1%)	13 (50%)	8 (31%)	5 (19%)
2017	2 (1-4)	78 (73-81)	4 (19,0%)	0	17 (81,0%)	17 (80%)	2 (10%)	2 (10%)
2018	5 (3-8)	76 (73-78)	7 (35,0%)	1 (5,0%)	12 (60,0%)	13 (65%)	2 (10%)	5 (25%)
2019	6 (2-12)	76 (70-79)	8 (24,2%)	1 (3,0%)	24 (72,7%)	21 (64%)	5 (15%)	7 (21%)
2020	4 (3-12)	74 (70-81)	5 (22,7%)	3 (16,6%)	14 (63,6%)	17 (77%)	2 (9%)	3 (14%)
2021	4 (2-6)	79 (65-79)	6 (31,6%)	0	13 (68,4%)	11 (58%)	3 (14%)	5 (26%)
p	0,0352	0,8539	0,7396			0,4606		

Table 2. Clinical manifestations categorized by year. Data expressed as *n* (%) or median (IQR)

However, there was a significant reduction in diagnostic latency time from 2016 to 2021, decreasing from 7 weeks to 4 weeks (p: 0.0352) (Table 2, Graph 1).



Graph 1. Diagnostic latency time (weeks)

1.3.4 DISCUSSION

GCA is a rare disease, and according to the guidelines of the Italian National Plan for Rare Diseases (2013-2016), patients with rare diseases must be centralized in third-level centers (expertise centers). They are also entitled to receive rare disease certificates and ticket exemptions, the issuance of which is validated by the relevant Local Health Authority (ATS) and monitored through an electronic registry.

The strength of this study lies in its use of the capture/recapture technique, integrating clinical hospital records with administrative registries from the ATS. Furthermore, the decision was made to utilize not only clinical data from the reference third-level center (which theoretically should already be responsible for all patients with rare diseases) but also to involve second-level centers at the territorial level. The objective was to avoid overlooking patients who, in clinical practice, may not be centralized due to age, comorbidities, and fragility, and who may not have been able to receive follow-up at the Spedali Civili but are managed in the periferical hospitals. If these patients were not considered, they could have represented a selection bias.

Over the six-year study period, the annual number of new GCA cases fluctuated considerably. The year 2021 saw the lowest number of new diagnoses (19), while 2019 recorded the highest, with 33 cases, accounting for 23.4% of the total. Previous studies conducted in various countries [3,7,94] had highlighted a cyclical pattern in GCA incidence. However, in the ATS Brescia region, despite these significant variations in annual case numbers, the study's limited timeframe did not allow for the identification of any clear trends, such as increases, decreases, or distinct peaks in incidence.

No significant variations were observed over time in clinical manifestations, age at diagnosis, gender distribution, or disease phenotype, consistent with previous Italian studies. However, the duration of the study period may represent a limitation for these analysis, as the analysis covered only a six-year interval between 2016 and 2021. It is possible that such a short time frame did not allow for the detection of significant changes in clinical presentation or diagnostic methods, which might have become apparent with the analysis of a longer time period.

On the other hand, a significant reduction in diagnostic latency from 2016 to 2021 was observed, defined as the number of weeks between symptom onset and GCA diagnosis. This outcome is likely attributable to increased awareness and understanding of the disease among healthcare personnel in the region.

1.3.5 CONCLUSIONS

The conclusions of this study on the epidemiology of GCA in the ATS Brescia region demonstrate that, although the disease remains rare, the approach used has allowed for a more accurate overview of its distribution and management within the area. The use of the capture/recapture technique, combining hospital clinical records and administrative records from the ATS, minimized the risk of missing cases. By involving not only the third-level reference center but also second-level centers in the territory, the study included patients who, due to age, comorbidities, or frailty, could not be centralized at Spedali Civili for follow-up. This strategy helped avoid a potential selection bias and provided a more reliable estimate of the incidence and clinical characteristics of GCA in the studied population.

The findings suggest that the epidemiology of GCA in the ATS Brescia region aligns with previous Italian cohorts and reflects a consistent clinical picture. However, despite covering a six-year period, the most significant change observed over time was a reduction in diagnostic latency, likely due to increased awareness and training among local healthcare professionals. Further studies conducted over a longer period may be necessary to identify potential changes in the clinical presentation or diagnostic approaches for GCA.

1.4 STUDY ON GIANT CELL ARTERITIS WITH LARGE VESSEL INVOLVEMENT AND ANALYSIS OF THIS SPECIFIC DISEASE SUBSET

1.4.1 AIM OF THE STUDY

In GCA, inflammation of the arterial branches of the carotid and vertebral arteries leads to the classic cranial symptoms of the disease, such as headache, jaw claudication, and blindness. However, in more than 50% of patients, there is involvement of the aorta and its major branches. This large vessel involvement results in a distinct and atypical clinical presentation, which is often more challenging to diagnose compared to the cranial form.

The aim of this study was to analyze a large cohort of GCA patients, comparing the clinical onset of those with large vessel involvement to those with the classic cranial symptoms. The aim was to better understand the differences in presentation and improve diagnostic approaches for the large vessel subset, which can often be under-recognized due to its more insidious onset and atypical manifestations. This could potentially lead to earlier detection and more tailored management strategies for patients with large vessel GCA, who might otherwise face delays in receiving the correct diagnosis and treatment.

1.4.2 METHODS

Patients were selected according to the following inclusion criteria: 1) patients with a new diagnosis of GCA made at Spedali Civili Brescia between January 1, 2005, and December 31, 2020, and meeting the 2022 ACR/EULAR classification criteria [59]; 2) complete medical history regarding disease onset; 3) a minimum follow-up of 6 months. The cohort was then stratified based on the clinical phenotype of GCA, with clinical and instrumental data obtained from both paper and electronic medical records.

Regarding the clinical phenotype, patients were categorized into those with cranial GCA (C-GCA), large vessel GCA (LV-GCA), and mixed GCA (LV-C GCA) phenotypes. This stratification was based on clinical and instrumental data. All

patients were required to meet the 2022 ACR/EULAR classification criteria (with a cumulative score of ≥6 points), and based on the criteria met, they were assigned to the respective phenotype. Specifically, the C-GCA phenotype was defined when some or all of the following 2022 ACR/EULAR classification criteria were satisfied: positive temporal artery biopsy or temporal artery halo sign on ultrasound (+5points); erythrocyte sedimentation rate (ESR) ≥50 mm/hour or C-reactive protein (CRP) ≥10 mg/L (+3); sudden visual loss (+3); morning stiffness in shoulders or neck (+2), jaw or tongue claudication (+2), new temporal headache. (+2), scalp tenderness (+2), temporal artery abnormality (+2).

The LV-GCA phenotype was defined when some or all of the following 2022 ACR/EULAR classification criteria were satisfied: ESR ≥50 mm/hour or CRP ≥10 mg/L (+3); morning stiffness in shoulders or neck (+2), bilateral axillary involvement on imaging (+2), and fluorodeoxyglucose-positron emission tomography (FDG-PET) activity throughout the aorta (+2). The LV-C-GCA phenotype was defined as the coexistence of criteria for both C-GCA and LV-GCA.

The statistical analysis began with the descriptive evaluation of variables, calculating the main indices of central tendency, expressed as median (1st-3rd interquartile), and percentage composition ratios. Differences between quantitative variables across patient groups were analyzed using the non-parametric Mann-Whitney test, while associations between nominal variables were assessed using the chi-square test or Fisher's exact test (if the expected frequency was <5). Correlations between clinical, biological, and instrumental markers, and disease subsets were evaluated through a series of simple linear regression analyses. A p-value ≤ 0.05 was considered statistically significant.

1.4.3 RESULTS

A total of 150 patients were enrolled in the study. Based on vascular involvement and following the classification criteria outlined in the Methods section, the patients were classified as follows: 22 patients had an LV-GCA clinical phenotype, 96 had C-GCA, and 32 had LV-C-GCA.

Demographic parameters are described in Table 3. Considering the entire cohort, 104 patients (69%) were female, and 46 (31%) were male. The median age at

diagnosis was 74 (67-78) years. When comparing demographic parameters across the three patient subgroups, a statistically significant difference was observed in age at diagnosis, but not in sex composition among the groups. Specifically, patients with predominant cranial involvement had a higher age at diagnosis compared to those with predominant extra-cranial involvement: 75 (70-80) years for C-GCA patients, 63 (60-75) for LV-GCA patients, and 72 (65-75) for LV-C-GCA patients. Diagnostic latency was defined as the time interval between symptom onset and GCA diagnosis. For the entire cohort, it was 5 (3-12) weeks, with a statistically significant difference between the patient groups. Patients with predominant cranial involvement had a shorter diagnostic latency, expressed in weeks, compared to those with predominant extra-cranial involvement: 4 (2-8) for C-GCA patients, 10 (4-17) for LV-C-GCA patients, and 13 (7-24) for LV-GCA patients.

Demographic	GCA (n: 150)	C-GCA (n: 96)	LV-GCA (n: 22)	C-LV-GCA (n: 32)	p
Sex (F/M)	104 (69,3%)/46 (30,7%)	66 (68,7%)/30 (31,3%)	16 (72,7%)/6 (27,3%)	22 (68,8%)/10 (31,2%)	0,9325
Age at diagnosis (years)	73,5 (67-78)	75,0 (70,0-79,5)	62,5 (59,5-75,0)	71,5 (65,0-75,0)	< 0,0001
Diagnostic latency	5,0 (3,0-12,0)	4,0 (2,0-8,0)	13,0 (7,2-24,0)	10,0 (4,0-16,5)	< 0,0001
Diagnostic setting (outpatient/ hospitalization	41 (27,3%)/109 (77,7%)	19 (19,8%)/77 (80,2%)	9 (40,9%)/13 (59,1%)	13 (40,6%)/19 (59,4%)	0,022

Table 3. Demographic characteristics categorized by vascular involvement. Data expressed as *n* (%) or median (IQR)

On the other hand, patients with cranial involvement had a higher frequency of hospitalization at the time of diagnosis compared to the other groups. In the entire cohort, 78% of patients were diagnosed during hospitalization, while 27% were diagnosed during outpatient evaluation without hospitalization. The distribution was different according to phenotype: in the C-GCA group, 80% of patients were hospitalized, while in the LV-GCA and LV-C-GCA groups, the hospitalization rate was 59% (p: 0.022).

The clinical presentation of patients and the main disease manifestations at the time of diagnosis are described in Table 4. For the entire cohort, the most common symptoms were headache (78%), fatigue (73%), weight loss (47%), PMR (47%), fever (42%), jaw claudication (43%), scalp tenderness (43%), ocular symptoms (37%), synovitis and/or arthritis (6%), chest pain (3%), abdominal claudication

(3%), limb claudication (3%), and cerebrovascular events (3%). Other less specific clinical symptoms or signs present at diagnosis included serositis (2 patients), carotidynia (2), dry cough (2), unilateral subclavian artery stenosis (1), vertigo (1), syncope (1).

When comparing clinical manifestations among the three patient groups, a significant difference in symptom frequency was noted, as expected. The most frequent symptoms in patients with exclusively cranial involvement (C-GCA) were headache (92%), fatigue (68%), jaw claudication (53%), ocular symptoms (50%), scalp tenderness (48%), fever (37%), weight loss (39%), synovitis and/or arthritis (5%), and cerebrovascular events (3%). The most frequent symptoms in patients with both cranial and extra-cranial involvement (LV-C-GCA) were fatigue (91%), headache (91%), PMR (56%), weight loss (54%), fever (53%), scalp tenderness (56%), jaw claudication (41%), ocular disturbances (22%), limb claudication (9%), chest pain (6%), cerebrovascular events (6%), and synovitis and/or arthritis (6%). The most frequent symptoms in patients with exclusively extra-cranial involvement (LV-GCA) were fatigue (73%), weight loss (64%), fever (50%), abdominal claudication (23%), PMR (23%), chest pain (14%), synovitis and/or arthritis (9%), and limb claudication (5%).

Clinical manifestations	GCA (n: 150)	C-GCA (n: 96)	LV-GCA (n: 22)	C-LV-GCA (n: 32)	p
Visual manifestations	55 (36,7%)	48 (50%)	0	7 (21,9%)	< 0,0001
Headache	117 (78,0%)	88 (91,7%)	0	29 (90,6%)	< 0,0001
Scalp tenderness	64 (42,7%)	46 (47,9%)	0	18 (56,2%)	< 0,0001
Jaw claudication	64 (42,7%)	51 (53,1%)	0	13 (40,6%)	< 0,0001
Limbs claudication	4 (2,7%)	0	1 (4,5%)	3 (9,4%)	0,0144
Thoracic pain	5 (3,3%)	0	3 (13,6%)	2 (6,2%)	0,0033
Claudicatio abdominis	5 (3,3%)	0	5 (22,7%)	0	< 0,0001
Stroke	4 (2,7%)	2 (2,1%)	0	2 (6,2%)	0,3148
Fever	10 (38,5%)	6 (28,6%)	6 (30,0%)	10 (30,3%)	1,0000
Weight loss	70 (46,7%)	37 (38,5%)	14 (63,6%)	19 (59,4%)	0,0278
Fatigue	110 (73,3%)	65 (67,7%)	16 (72,7%)	29 (90,6%)	0,0398
PMR	70 (46,7%)	47 (49,0%)	5 (22,7%)	18 (56,2%)	0,0398

Table 4. Clinical manifestations categorized by vascular involvement. Data expressed as *n* (%) or median (IQR)

Laboratory, histological, and imaging parameters at the time of diagnosis are described in Table 5. The median values of CRP and ESR were 80 (43-127) mg/ml and 68 (46-88) mm/h, respectively. Of the 123 patients with complete biochemical exams available prior to GC therapy, 52 (42%) had leukocytosis, 92 (75%) had anemia, and 47 out of 117 patients (420%) had thrombocytosis. No statistically significant differences were found regarding laboratory parameters, including inflammatory markers. In the entire cohort, 34 patients performed a temporal artery ultrasound, of which 19 (56%) positives for halo sign and 87 performed a temporal artery biopsy (TAB), of which 68 positives at histological examination. In particular, TAB histological analysis showed 56 (82%) transmural inflammation (TMI) patterns, 9 (13%) inflammation limited to adventitia (ILA) patterns, 2 (3%) small vessel vasculitis (SVV) patterns, and 1 non-specific pattern. In the C-GCA group, 70 patients underwent a temporal artery biopsy, of which 59 showed positive results on histological examination. Patients with negative biopsy results were also considered as having C-GCA if they met the inclusion criteria based on clinical symptoms. The negative findings were attributed to the possible effects of ongoing steroid treatment or the well-known patchy nature of vessel inflammation in this disease.

Moreover, 81 patients performed an 18-fluorodeoxyglucose positron emission tomography (18FDG-PET)/computed tomography (CT), of which 52 (64%) positives. In patients with large vessels involvement (LV-GCA and LV-C-GCA) thoracic aorta, subclavian arteries and abdominal aorta were the most frequently involved arteries.

Laboratory and imaging	GCA (n: 150)	C-GCA (n: 96)	LV-GCA (n: 22)	C-LV-GCA (n: 32)	p
CRP (mg/ml)	80 (43-127)	77 (41-121)	106 (44-127)	106 (67-135)	0,1738
ESR (mm/h)	68 (46-88)	68 (46-88)	78 (51-88)	66 (45-89)	0,7423
Leukocytosis	52/123 (42%)	34/82 (42%)	8/18 (44%)	10/23 (44%)	0,9654
White blood cells count (cell/μl)	9320 (7385-11525)	8720 (7035-11400)	9460 (7493-12210)	9710 (8335-10975)	0,5331
Anemia	92/123 (75%)	59/82 (72%)	14/18 (78%)	19/23 (83%)	0,5539
Red blood cell count (cell*10^6/μl)	4,0 (3,7-4,5)	4,1 (3,8-4,6)	4,3 (4,0-4,5)	3,9 (3,6-4,1)	0,1418
Hb (g/dL)	11,6 (10,5-12,6)	11,7 (10,8-12,8)	11,7 (9,5-12,3)	10,7 (9,5-12,2)	0,0814
Thrombocytosis	47/117 (40%)	31/76 (41%)	6/18 (33%)	10/23 (44%)	0,7918
Platelet count (cell*10^3/μl)	364 (309-441)	363,5 (297-447)	341,5 (288-411)	372,0 (355-422)	0,4883
Positive TA biopsy	68/87 (78,2%)	59/70 (84,3%)	0/4	9/13 (69,2%)	0,0003
Positive TA CDUS	19/34 (55,9%)	9/21 (42,9%)	0/1	10/12 (83,3%)	0,0412
Positive PET/CT	52/81 (64,2%)	2/30 (6,7%)	20/21 (95,2%)	30/30 (100%)	< 0,0001

Table 5. Laboratory and imaging finding at diagnosis categorized by vascular involvement. CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; TA: Temporal Artery. Data expressed as *n* (%) or median (IQR)

1.4.4 DISCUSSION

GCA presents with three distinct clinical phenotypes, each characterized by specific clinical features that differentiate them from one another. This study aimed to examine these phenotypes and to assess the clinical presentation, diagnostic latency, and hospitalization rates among these groups.

When comparing clinical manifestations, it was found that certain systemic symptoms, such as fatigue and weight loss, were more frequently observed in patients with LV-GCA. These symptoms reflect the systemic inflammatory nature of the disease and the involvement of larger arteries like the aorta and its major branches. In contrast, fever, another common systemic symptom, was equally reported across all three phenotypic groups, suggesting that systemic inflammation is a shared feature regardless of the pattern of vascular involvement.

Polymyalgia rheumatica (PMR) was more common in patients with C-GCA, associated with symptoms associated with the localized inflammation of the cranial arteries, particularly the branches of the carotid artery. This involvement leads to

the classic cranial symptoms of GCA, including headache, scalp tenderness, ocular involvement, and jaw claudication.

On the other hand, patients in the LV-GCA and LV-C-GCA groups more commonly reported symptoms related to large-vessel involvement, such as chest pain, limb claudication, and abdominal claudication, reflecting thoracic aorta, subclavian artery, and abdominal aorta involvement. These symptoms are more indicative of vascular involvement in the large arteries, and they present a more insidious clinical picture compared to the acute cranial symptoms seen in C-GCA. Despite these differences in clinical presentation, there were no statistically significant differences between the groups regarding laboratory parameters, including inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). This indicates that while clinical manifestations differ, the inflammatory burden measured by laboratory tests remains similar across phenotypes.

A notable finding was the shorter duration of symptoms prior to diagnosis in patients with C-GCA compared to those with LV-GCA or LV-C-GCA. This is likely due to the more striking and recognizable nature of cranial symptoms, which prompt earlier medical attention. Cranial symptoms like sudden visual loss, severe headache, and jaw claudication are alarming to both patients and healthcare providers, facilitating quicker diagnosis and treatment. However, patients with C-GCA also showed a higher frequency of hospitalization at the time of diagnosis, with 80% of these patients requiring hospital admission. This may suggest that while these patients present with a more acute clinical picture, the severity of their symptoms, particularly the risk of vision loss, often necessitates immediate hospitalization for urgent management. In contrast, patients with LV-GCA, who typically present with more nonspecific systemic symptoms, often experience longer diagnostic delays. These symptoms—such as fatigue, weight loss, and mild fever—are less specific and may be attributed to other, more common conditions, delaying the recognition of large-vessel involvement. Additionally, large-vessel involvement often requires advanced imaging techniques, such as PET-CT, for confirmation, which may further contribute to diagnostic delays.

A limitation of the study is that not all patients with C-GCA underwent a PET scan; therefore, there might be patients with LV-C-GCA within the C-GCA cohort. This could introduce a bias in patient classification, although limited to a small number of patients.

1.4.5 CONCLUSIONS

This study underscores significant differences in the clinical presentation of the various phenotypes of GCA. Patients with the cranial form of GCA typically present with acute cranial symptoms, which lead to a faster diagnosis and higher hospitalization rates due to the severity of the clinical presentation, particularly the risk of irreversible vision loss. In contrast, patients with large-vessel GCA experience longer diagnostic latency, likely due to their more subtle and nonspecific symptoms. Systemic signs such as fatigue and weight loss, which are common in LV-GCA, may not initially raise clinical suspicion for vasculitis, contributing to delayed diagnosis.

These findings highlight the importance of maintaining a high degree of clinical suspicion, especially in patients with systemic symptoms that could mask the underlying involvement of large vessels. A timely and accurate diagnosis is crucial to prevent complications and improve outcomes in GCA patients. In this context, an aggressive diagnostic approach, including advanced imaging for large-vessel involvement, becomes essential, particularly in patients who may not present with the classic cranial symptoms of GCA.

In conclusion, large-vessel GCA appears to be a distinct subset of the disease with different clinical manifestations compared to the more classic form of GCA. Current literature and randomized controlled trials (RCTs) involving GCA patients have typically treated the disease as a single entity, irrespective of the type of vascular involvement. However, the findings from this study suggest that LV-GCA represents a specific clinical subset, which could potentially differ from other forms in terms of disease progression, the risk of relapses, and treatment responses. Further studies are needed to investigate whether these patients require tailored therapeutic strategies and closer monitoring.

1.4.6 PUBLICATIONS ON THE TOPIC

1) Regola F, Bosio G, Andreoli L, Franceschini F, Toniati P. Clinical Features at Disease Onset of Different Subsets of Large-vessel-giant Cell Arteritis in a Monocentric Cohort of 100 Patients. Arthritis Rheumatol. 2021; 73 (suppl 9). https://acrabstracts.org/abstract/clinical-features-at-disease-onset-of-different-subsets-of-large-vessel-giant-cell-arteritis-in-a-monocentric-cohort-of-100-patients/

2) Regola F, Franceschini F, Bosio G, Toniati P. POS0797 Large Vessel-GCA: a diagnostic challenge. Annals of the Rheumatic Diseases 2021;80:650-651. https://ard.bmj.com/content/80/Suppl_1/650.2

ABSTRACT NUMBER: 1409

Clinical Features at Disease Onset of Different Subsets of Large-vessel-giant Cell Arteritis in a Monocentric Cohort of 100 Patients

Francesca Regola[1], Giovanni Bosio[2], Laura Andreoli[3], Franco Franceschini[1] and Paola Toniati[1], [1]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili and University of Brescia, Brescia, Italy, [2]Nuclear Medicine Unit, ASST Spedali Civili of Brescia, Brescia, Italy, [3]University of Brescia, Brescia, Italy

Meeting: ACR Convergence 2021

Keywords: giant cell arteritis, Vasculitis

SESSION INFORMATION

Date: Monday, November 8, 2021

Session Type: Poster Session C

Title: Vasculitis – Non-ANCA-Associated & Related Disorders Poster I: Giant Cell Arteritis & Polymyalgia Rheumatica (1391–1419)

Session Time: 8:30AM-10:30AM

Background/Purpose: Giant Cell Arteritis (GCA) is the most frequent systemic vasculitis in patients older than 50 years involving medium-sized and large arteries. Inflammation of the extracranial branches of the carotid artery gives rise to the classic symptoms of GCA. However, GCA involves also the aorta and its major branches in almost two-thirds of patients (1,2). Large vessel involvement leads to a different atypical clinical picture which can be challenging to diagnose (3). More information on clinical presentation and vessel involvement in large-vessel GCA are needed to better diagnose it. The aim of this study is to analyze a large cohort of GCA comparing patients with large-vessel involvement to patients with classical cranial disease.

Methods: 100 consecutive patients with a clinical diagnosis of GCA were enrolled in this retrospective study. All patients were older than 50 years of age, met the ACR criteria for GCA (4) or had a positive temporal artery biopsy or evidence of large vessel vasculitis at FDG-PET/CT scan.

Results: Based on vascular involvement, patients were classified into three group: 61 patients with only cranial arteritis (C-GCA), 16 patients with only extracranial large vessel vasculitis (LV-GCA) and 23 patients with both cranial and large vessel involvement (LV-C-GCA).

Compared to C-GCA, patients with large vessel involvement (LV-GCA and LV-C-GCA) were younger and more frequently women, and the difference was further significant for patients with isolated LV-GCA. Patients with isolated LV-GCA had also the longer duration of symptoms at GCA diagnosis [LV-GCA 20(16-82) vs LV-C-GCA 12(4-16) vs C-GCA 4(3-12) weeks; $p< 0.001$]. Systemic symptoms, as fever and fatigue, were associated with large vessel involvement, both in LV-GCA and LV-C-GCA groups. Polymyalgia rheumatica was equally reported in all three groups and no significant differences were found in inflammatory markers levels according to vessel involvement. In patients with large vessels

involvement (LV-GCA and LV-C-GCA) thoracic aorta, subclavian arteries and abdominal aorta were the most frequently involved arteries.

Conclusion: GCA is not a single entity but includes several patterns of disease. Female gender, younger age and systemic symptoms are associated with large vessel involvement, regardless the presence or absence of cranial symptoms. The different clinical manifestations of large vessel GCA lead to a longer time to diagnosis if compared to C-GCA. For these reasons, in patients with the aforementioned characteristics, a large vessel involvement should be considered in order to reduce the time to diagnosis.

1: De Boysson H, et al. Clin Exp Rheumatol 2019; 2: Prieto-González S, et al. Ann Rheum Dis 2012; 3: Muratore F, et al. Rheumatol 2015; 4: Hunder GG, et al. Arthritis Rheum 1990

	GCA (n: 100)	C-GCA (n: 61)	LV-C-GCA (n: 23)	LV-GCA (n: 16)	*p*
Age: median (IQR)	76 (67-79)	75 (71-80)	74 (69-77)	63 (59-72)	0.001
Female	68 (68%)	38 (62%)	17 (74%)	13 (81%)	0.276
Male	32 (32%)	23 (38%)	6 (26%)	3 (19%)	0.276
Time between symptom onset and diagnosis (weeks)	8 (4-20)	4 (3-12)	12 (4-16)	20 (16-82)	<0.001
Cranial symptoms (overall)	84 (84%)	61 (100%)	23 (100%)	0 (0%)	<0.001
New temporal headache	77 (77%)	58 (95%)	19 (83%)	0 (0%)	<0.001
Visual symptoms	39 (39%)	34 (56%)	5 (22%)	0 (0%)	<0.001
Jaw or tongue claudication	35 (35%)	27 (44%)	8 (35%)	0 (0%)	0.004
Fever	48 (48%)	23 (38%)	14 (61%)	11 (69%)	0.032
Fatigue	75 (75%)	40 (66%)	21 (91%)	14 (88%)	0.023
Weight loss	52 (52%)	28 (46%)	13 (57%)	11 (69%)	0.235
Polymyalgia rheumatica	43 (43%)	27 (44%)	13 (57%)	3 (19%)	0.061
Arm or leg claudication	5 (5%)	0 (0%)	4 (17%)	1 (6%)	0.005
CRP (C-reactive protein)	83 (45-127)	77 (39-115)	89 (50-134)	95 (20-124)	0.461
ESR (erythrocyte sedimentation rate)	72 (47-96)	70 (46-88)	75 (28-105)	66 (44-91)	0.711
Cranial arteries	84 (84%)	61 (100%)	23 (100%)	0 (0%)	<0.001
Carotid arteries	19 (19%)	0 (0%)	12 (52%)	7 (44%)	<0.001
Subclavian and upper limb arteries	21 (21%)	0 (0%)	10 (43%)	11 (69%)	<0.001
Thoracic aorta	29 (29%)	0 (0%)	15 (65%)	14 (88%)	<0.001
Abdominal aorta	21 (21%)	0 (0%)	10 (43%)	11 (69%)	<0.001
Iliac and inferior limb arteries	10 (10%)	0 (0%)	6 (26%)	4 (25%)	<0.001

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POS0797 **LARGE VESSEL-GCA: A DIAGNOSTIC CHALLENGE**

F. Regola[1], F. Franceschini[1], G. Bosio[2], P. Toniati[1]. *[1]ASST Spedali Civili and University of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy*; *[2]ASST Spedali Civili, Nuclear Medicine Unit, Brescia, Italy*

Background: GCA is the most frequent systemic vasculitis in patients older than 50 years involving medium-sized and large arteries. Inflammation of the extracranial branches of the carotid artery gives rise to the classic symptoms of GCA. However, in almost two-thirds of patients GCA involves also the aorta and its major branches (1,2). Large vessel involvement leads to a different atypical clinical picture which can be challenging to diagnose (3,4). More information on clinical presentation and vessel involvement in large-vessel GCA are needed to better diagnose it.

Objectives: To analyze clinical presentation of large-vessel GCA compared to classical cranial disease.

Methods: 100 consecutive patients with a clinical diagnosis of GCA were enrolled in this retrospective study. All patients were older than 50 years of age, met the ACR criteria for GCA or had a positive biopsy of the temporal artery or evidence of large vessel vasculitis at FDG-PET/CT scan.

Results: Based on vascular involvement, patients were classified into three group: 61 patients with only cranial arteritis (C-GCA), 16 patients with only extracranial large vessel vasculitis (LV-GCA) and 23 patients with both cranial and large vessel involvement (LV-C-GCA).

Compared to C-GCA, patients with large vessel involvement (LV-GCA and LV-C-GCA) were younger and more frequently women, and the difference was further significant for patients with isolated LV-GCA. Patients with isolated LV-GCA had also the longer duration of symptoms at GCA diagnosis [LV-GCA 20(16-82) *vs* LV-C-GCA 12(4-16) *vs* C-GCA 4(3-12) weeks; p<0.001]. Systemic symptoms, as fever and fatigue, were associated with large vessel involvement, both in LV-GCA and LV-C-GCA groups. Polymyalgia rheumatica was equally reported in all three cohorts of patients and no significant differences were found in inflammatory markers levels according to vessel involvement.

In patients with large vessels involvement (LV-GCA and LV-C-GCA) thoracic aorta, subclavian arteries and abdominal aorta were the most frequently involved arteries.

Conclusion: GCA is not a single entity but includes several patterns of disease. Female gender, younger age and systemic symptoms are associated with large vessel involvement, regardless the presence or absence of cranial symptoms. The different clinical manifestations of large vessel GCA lead to a longer time to diagnosis if compared to C-GCA. For these reasons, in patients with the aforementioned characteristics, a large vessel involvement should be considered in order to reduce the time to diagnosis.

REFERENCES:

[1] De Boysson H, et al. Clin Exp Rheumatol 2019.
[2] Prieto-González S, et al. Ann Rheum Dis 2012.
[3] Brack A, et al. Arthritis Rheum 1999.
[4] Muratore F, et al. Rheumatol 2015.

	GCA (n: 100)	C-GCA (n: 61)	LV-C-GCA (n: 23)	LV-GCA (n: 16)	p
Age: median (IQR)	76 (67-79)	75 (71-80)	74 (69-77)	63 (59-72)	0.001
Female/ Male	68 (68%) / 32 (32%)	38 (62%) / 23 (38%)	17 (74%) / 6 (26%)	13 (81%) / 3 (19%)	0.276
Time between symptom onset and diagnosis (weeks)	8 (4-20)	4 (3-12)	12 (4-16)	20 (16-82)	<0.001
Cranial symptoms (overall)	84 (84%)	61 (100%)	23 (100%)	0 (0%)	<0.001
New temporal headache	77 (77%)	58 (95%)	19 (83%)	0 (0%)	<0.001
Visual symptoms	39 (39%)	34 (56%)	5 (22%)	0 (0%)	<0.001
Jaw or tongue claudication	35 (35%)	27 (44%)	8 (35%)	0 (0%)	0.004
Fever	48 (48%)	23 (38%)	14 (61%)	11 (69%)	0.032
Fatigue	75 (75%)	40 (66%)	21 (91%)	14 (88%)	0.023
Weight loss	52 (52%)	28 (46%)	13 (57%)	11 (69%)	0.235
Polymyalgia rheumatica	43 (43%)	27 (44%)	13 (57%)	3 (19%)	0.061
Arm or leg claudication	5 (5%)	0 (0%)	4 (17%)	1 (6%)	0.005
CRP (C-reactive protein)	83 (45-127)	77 (39-115)	89 (50-134)	95 (20-124)	0.461
ESR (erythrocyte sedimentation rate)	72 (47-96)	70 (46-88)	75 (28-105)	66 (44-91)	0.711
Cranial arteries	84 (84%)	61 (100%)	23 (100%)	0 (0%)	<0.001
Carotid arteries	19 (19%)	0 (0%)	12 (52%)	7 (44%)	<0.001
Subclavian and upper limb arteries	21 (21%)	0 (0%)	10 (43%)	11 (69%)	<0.001
Thoracic aorta	29 (29%)	0 (0%)	15 (65%)	14 (88%)	<0.001
Abdominal aorta	21 (21%)	0 (0%)	10 (43%)	11 (69%)	<0.001
Iliac and inferior limb arteries	10 (10%)	0 (0%)	6 (26%)	4 (25%)	<0.001

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1.5 STUDY ON RISK FACTORS FOR THE DEVELOPMENT OF BLINDNESS IN GIANT CELL ARTERITIS

1.5.1 AIM OF THE STUDY

In GCA ocular symptoms are a common and severe manifestation, occurring in more than one-third of GCA patients. These symptoms result from ischemic damage to the optic nerve, typically caused by the involvement of one or more branches of the ophthalmic artery. Most patients initially present with transient vision loss, known as amaurosis fugax, which can be monocular or binocular. In addition, peripheral visual field narrowing or blurred vision may occur as part of the early symptoms. Once vision loss is established, it is rarely reversible, making early recognition of premonitory symptoms crucial for timely intervention. If left untreated, progressive arterial occlusion leads to irreversible ischemic damage, culminating in permanent vision loss. This vision impairment can be either partial or complete, affecting one or both eyes.

Notably, monocular blindness - and even more so binocular blindness - is associated with significant disability, reduction in both quality of life and life expectancy. Blindness is one of the most feared complications of GCA among patients. Vision-related quality of life is a primary concern for these individuals, as the condition profoundly affects their physical and emotional well-being. Several features of giant cell arteritis, including vision loss, significantly impact patients' global quality of life, underscoring the need for prompt and effective management [95].

Although several studies have sought to identify risk factors for blindness in GCA, the only consistently proven factor to date is the presence of amaurosis and other ischemic symptoms in the days preceding the development of irreversible blindness [96]. This study aims to further investigate potential risk factors for blindness in a cohort of GCA patients, with the goal of improving early recognition and treatment to prevent this debilitating complication.

1.5.2 METHODS

Patients were selected according to the following inclusion criteria, above mentioned for the study "Study on Giant Cell Arteritis with Large Vessel

Involvement and analysis of this specific disease subset": 1) patients with a new diagnosis of GCA made at Spedali Civili Brescia between January 1, 2005, and December 31, 2020, and meeting the 2022 ACR/EULAR classification criteria [59]; 2) complete medical history regarding disease onset; 3) a minimum follow-up of 6 months. Among the identified patients who met the criteria, only those with a cranial involvement (C-GCA and LV-C phenotypes) were selected. Specifically, the cranial involvement was defined when some or all of the following 2022 ACR/EULAR classification criteria were satisfied (with a cumulative score of ≥6 points): positive temporal artery biopsy or temporal artery halo sign on ultrasound (+5points); erythrocyte sedimentation rate (ESR) ≥50 mm/hour or C-reactive protein (CRP) ≥10 mg/L (+3); sudden visual loss (+3); morning stiffness in shoulders or neck (+2), jaw or tongue claudication (+2), new temporal headache. (+2), scalp tenderness (+2), temporal artery abnormality on vascular examination (+2). The patients were then classified into two groups: with or without ocular involvement. Those with ocular involvement were defined as patients who presented at least one of the following symptoms and had undergone an ophthalmological evaluation that excluded other causes of such symptoms: blurred vision, diplopia, amaurosis fugax, partial visual loss in one or both eyes, and complete vision loss in one or both eyes. Clinical and instrumental data obtained from both paper and electronic medical records.

The statistical analysis began with the descriptive evaluation of variables, calculating the main indices of central tendency, expressed as median (1st-3rd interquartile), and percentage composition ratios. Differences between quantitative variables across patient groups were analyzed using the non-parametric Mann-Whitney test, while associations between nominal variables were assessed using the chi-square test or Fisher's exact test (if the expected frequency was <5). A p-value ≤ 0.05 was considered statistically significant.

1.5.3 RESULTS

A total of 128 patients with GCA and cranial involvement were enrolled in the study (96 with C-GCA phenotype, and 32 with LV-C-GCA). The median age at diagnosis was 74 (67-78) years, 88 patients (69%) were female, and 40 (31%) were male.

Overall, 55 patients presented with ocular involvement (48 C-GCA and 7 LV-C-GCA), with the most frequently reported symptoms being blurred vision (6 patients), diplopia (6), amaurosis fugax (5), monocular partial visual loss (21), binocular partial visual loss eyes (2), monocular complete blindness (12) and binocular complete blindness (3). Out of 38 patients with partial or complete visual loss, 36 presented Arteritic Anterior Ischemic Optic Neuropathy (AION), while Central Retinal Artery Occlusion (CRAO) was seen in 2 of them.

Patients with visual manifestations had a median (IQR) age of 77 (73-81) years, significantly older if compared to patients without ocular symptoms (72 (67-76) years, $p<0.001$), while gender was not associate with higher or lower risk (Table 6). Comorbidities at the time of diagnosis were compared between the two groups to assess whether they were associated with an increased risk of developing visual impairment. Patients with ocular involvement presented more often hypertension (67 vs 44%, p: 0.0085) and chronic kidney disease (7 vs 0%, p: 0.0315), while no differences were found in diabetes, cancer, coronary heart disease and dyslipidemia incidence. In the subsequent multivariate analysis, hypertension and age at diagnosis retained statistical significance.

Demographic	GCA (n: 128)	Ocular involvement (n: 55)	NO ocular involvement (n: 73)	p
Sex (F/M)	88 (69%)/40 (31%)	36 (65%)/19 (35%)	52 (71%)/21(29%)	0,4875
Age at diagnosis (years)	74 (67-78)	77 (73-81)	72 (67-76)	< 0,0001
Smoke	31 (24%)	9 (16%)	22 (30%)	0,0718
Diabetes	13 (10%)	7 (13%)	6 (8%)	0,4032
Cancer	17 (13%)	9 (16%)	8 (11%)	0,3724
Hypertension	69 (54%)	37 (67%)	21 (44%)	0,0085
Chronic kidney disease	4 (3%)	4 (7%)	0 (0%)	0,0315
Coronary heart disease	16 (13%)	8 (15%)	8 (11%)	0,5436
Dyslipidemia	32 (25%)	15 (27%)	17 (23%)	0,6063

Table 6. Demographic characteristics. Data expressed as *n* (%) or median (IQR)

The clinical presentation and main disease manifestations at the time of diagnosis are detailed in Table 7. In the entire cohort, the most frequent symptoms were headache (91%), fatigue (73%), scalp tenderness (50%), jaw claudication (50%), and polymyalgia rheumatica (PMR) (51%). When comparing the clinical

manifestations between the two patient groups, no significant differences were observed in the frequency of cranial symptoms (headache, scalp tenderness, jaw claudication, stroke) or systemic manifestations (fever, weight loss, fatigue, PMR). However, the presence of peripheral arthritis was inversely associated with ocular involvement. No statistically significant differences were found regarding laboratory parameters, including inflammatory markers (Table 8).

Clinical manifestations	GCA (n: 128)	Ocular involvement (n: 55)	NO ocular involvement (n: 73)	p
Headache	117 (91%)	52 (95%)	65 (89%)	0,2714
Scalp tenderness	64 (50%)	27 (49%)	37 (51%)	0,8583
Jaw claudication	64 (50%)	27 (49%)	37 (51%)	0,8583
Stroke	4 (3%)	2 (4%)	2 (3%)	0,7729
Fever	52 (41%)	18 (33%)	34 (47%)	0,1143
Weight loss	56 (44%)	21 (38%)	35 (48%)	0,2703
Fatigue	94 (73%)	39 (71%)	55 (75%)	0,5740
PMR	65 (51%)	28 (51%)	37 (51%)	0,9800
Arthritis	7 (5%)	0 (0%)	7 (10%)	0,0182

Table 7. Clinical manifestations. Data expressed as *n* (%).

Laboratory	GCA (n: 128)	Ocular involvement (n: 55)	NO ocular involvement (n: 73)	p
CRP (mg/ml)	79 (43-126)	76 (39-119)	88 (53-133)	0,1846
ESR (mm/h)	67 (46-88)	65 (48-91)	69 (45-86)	0,7913
White blood cells count (cell/μl)	9329 (7370-11240)	8595 (7275-10770)	9480 (7545-11660)	0,2585
Red blood cell count (cell*10^6/μl)	4000 (3747-4392)	4030 (3682-4382)	3990 (3752-4380)	0,9558
Hb (g/dL)	11,6 (10,5-12,6)	11,6 (10,5-12,4)	11,6 (10,6-12,8)	0,7804
Platelet count (cell*10^3/μl)	372 (310-443)	358 (275-440)	373 (323-452)	0,3303

Table 8. Laboratory finding at diagnosis. CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; TA: Temporal Artery. Data expressed as *n* (%) or median (IQR)

1.5.4 DISCUSSION

The first documented case of visual loss in GCA was reported by Jennings in 1938, where a 66-year-old woman suffered complete blindness in her left eye due to retinal artery occlusion [97]. Before the widespread use of glucocorticoids, studies indicated a high prevalence of visual complications, affecting almost 60% of patients [98,99]. However, the introduction of glucocorticoid therapy has significantly reduced the incidence of vision loss to around 10-20%, with a downward trend observed in recent years [100]. Despite these improvements, vision loss remains one of the most severe and feared complications of GCA, even 90 years after Jennings' report. Blindness leads to profound disability, adversely affecting both quality of life and life expectancy.

Given the severe impact of visual loss, it remains essential to identify reliable prognostic factors for ocular involvement even today. However, to date, no definite methods for assessing risk factors for permanent visual impairment in GCA have been established While various potential risk factors - such as advanced age, hypertension, elevated platelet count, and jaw claudication - have been proposed, findings across studies remain inconsistent [32,101,102].

The most consistently recognized risk factor for predicting irreversible vision impairment in GCA patients is a history of transient visual loss [103]. However, this symptom already indicates ischemic involvement of the optic nerve, representing a late-stage marker of the disease.

This study aimed to address unresolved questions related to ocular involvement in GCA by analyzing a large, well-characterized cohort with long-term follow-up. Additionally, we incorporated recent evidence highlighting the importance of differentiating between GCA phenotypes, particularly cranial and large-vessel involvement. While these phenotypes share common features, they exhibit significant differences. Ocular involvement is predominantly linked to cranial manifestations, making these patients the key focus of investigation. For this reason, only patients with pure cranial or mixed cranial and large-vessel involvement (C-GCA or LV-C GCA) were included, while those with exclusive large-vessel involvement were excluded.

Our analysis revealed no significant differences in the frequency of cranial symptoms (headache, scalp tenderness, jaw claudication, stroke) or systemic manifestations (fever, weight loss, fatigue, PMR) between patients with and without ocular involvement. Likewise, no statistically significant differences were observed in laboratory parameters, including inflammatory markers. However, one notable finding was that peripheral arthritis appeared inversely associated with ocular involvement.

Hypertension and chronic kidney disease, on the other hand, were significantly more common in patients with ocular involvement than those without. Other previous studies have suggested that hypertension and a history of ischemic heart disease may increase the risk of severe ischemic complications in GCA, although not all studies have confirmed this [37,102]. One study found a positive association between traditional atherosclerosis risk factors and GCA-related ischemic events, proposing that patients with atherosclerosis might have impaired angiogenic compensatory mechanisms [104]. This is consistent with our study, were age, hypertension and chronic kidney disease, three well-known predisposing factors for atherosclerosis, resulted associated with ocular involvement.

These findings could support the implementation of preventive strategies based on the identified risk factors. A detailed analysis of a patient's risk profile at diagnosis may help identify those at higher risk of developing blindness, allowing for heightened vigilance and tailored care. For instance, from the time of diagnosis, serial ophthalmological evaluations could be initiated to detect early, presymptomatic visual impairment. Furthermore, educating patients on warning symptoms, such as sudden visual changes, could facilitate timely intervention.

Currently, there is insufficient evidence to recommend a distinct therapeutic approach for these high-risk patients. However, it is known that ocular manifestations often require more intensive immunosuppressive therapy. It is therefore conceivable that for patients identified as high risk, treatment adjustments could be considered—such as a slower tapering of corticosteroids or earlier introduction of immunosuppressive agents.

1.5.5 CONCLUSIONS

In this large cohort of GCA patients, partial or complete visual loss emerged as the most frequent visual complication. Notably, no significant associations were found between ocular involvement and other cranial or systemic symptoms. However, patients with peripheral arthritis appeared to have a reduced risk of developing visual impairment.

Age, hypertension and chronic kidney disease at disease onset were identified as the most significant risk factors for ischemic ocular manifestations in GCA. These findings highlight the critical role of cardiovascular comorbidities in the development of visual complications, emphasizing the need for a more holistic approach to managing these risk factors. Addressing hypertension and related conditions could potentially lower the incidence of vision loss in patients with GCA, improving overall outcomes.

1.5.6 PUBLICATIONS ON THE TOPIC

1) Regola F, Mora J, Franceschini F, et al. AB0744 Hypertension and age are risk factors for visual impairment in Giant Cell Arteritis. Annals of the Rheumatic Diseases 2023;82:1578. https://doi.org/10.1136/annrheumdis-2023-eular.3686

AB0744 **HYPERTENSION AND AGE ARE RISK FACTORS FOR VISUAL IMPAIRMENT IN GIANT CELL ARTERITIS**

Keywords: Vasculitis

F. Regola[1,2], J. Mora[1,2], F. Franceschini[1,2], P. Toniati[1]. [1]*ASST Spedali Civili of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy*; [2]*University of Brescia, Department of Clinical and Experimental Sciences, Brescia, Italy*

Background: Permanent vision loss is a feared complication and a leading cause of morbidity in Giant Cell Arteritis (GCA). Prompt recognition of patients with visual manifestation is fundamental to reduce permanent vision loss occurrence.
Objectives: The study aims to evaluate risk factors for visual manifestations at disease onset in an Italian monocentric cohort of patients with Giant Cell Arteritis (GCA).
Methods: We identified 128 patients with GCA diagnosed between 2011 and 2021 in our Center. All patients were older than 50 years of age, met the 1990 ACR criteria for GCA or had a positive temporal artery biopsy or ultrasound. Medical records of all patients were reviewed and demographic, clinical, and laboratory data were collected.
Results: Fifty-five patients (43%) presented at diagnosis visual ischemic manifestations: blurred vision in 6 pts, diplopia in 6 pts, amaurosis fugax in 5 pts, partial visual loss in 23 pts and complete vision loss in 1 or 2 eyes in 12 and 3 pts respectively. Out of 38 patients with partial or complete visual loss, 36 presented Arteritic Anterior Ischemic Optic Neuropathy (AION), and 2 presented Central Retinal Artery Occlusion (CRAO). Patients with visual manifestations had a median age of 77 (IQR 73-81) years, significantly older if compared to patients without ocular symptoms (72 (67-76) years, p<0.001). Patients with ocular involvement presented more often hypertension (67 vs 44%, p: 0.009) and chronic kidney disease (7 vs 0%, p: 0.031) as comorbidity at diagnosis, while no differences were found in diabetes, cancer, coronary heart disease and dyslipidemia incidence comparing patients with and without visual manifestations.
No associations between visual impairment and other cranial symptoms (headache, jaw claudication, scalp tenderness) were found, but peripheral arthritis was negatively associated with ocular manifestations. No laboratory variables were associated with ocular involvement.
Conclusion: In this large cohort of patients with GCA, partial or complete visual loss were the most frequent visual manifestations. No associations between ocular involvement and other cranial symptoms were found, while patients with peripheral arthritis had a lower risk of developing visual impairment. Age and hypertension at disease onset seem to be the most important risk factors for visual ischemic manifestations in GCA patients.

REFERENCES:

[1] Liozon E et al. J Rheumatol 2016. [2] Baalbaki H et al. Clin Rheumatol 2021.

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1.6 STUDY ON PREVALENCE AND CAUSES OF HOSPITALIZATION AND MORTALITY IN GIANT CELL ARTERITIS

1.6.1 AIM OF THE STUDY

GCA is a severe inflammatory disease that can lead to serious complications, such as visual loss, cerebrovascular accidents, and aortic aneurysms. Due to the risk of irreversible complications, the treatment of GCA necessitates the use of high-dose glucocorticoids and other immunosuppressive therapies. While these treatments are critical for preventing severe outcomes, they are also associated with significant adverse effects, including infections, osteoporosis, diabetes, and cardiovascular complications. Despite these associated risks, mortality in patients with GCA does not seem to differ significantly from that of the general population [105–107]. However, GCA patients, being part of an older and generally frail demographic, are particularly vulnerable to complications that may necessitate hospitalization. This increased risk of hospitalization may be attributed not only to disease-related complications but also to the adverse effects of prolonged and high-dose glucocorticoid and immunosuppressive therapy.

To date, there have been only three studies examining the patterns of hospitalization in GCA patients, all of which have been conducted in the United States [108–110]. These studies rely solely on epidemiological registries, where hospitalizations are coded using administrative systems, such as the International Classification of Diseases (ICD). While these registries provide valuable population-level data, they are prone to potential coding errors, which may lead to inaccuracies in reporting the true burden of hospitalizations in GCA. Moreover, these studies focus on hospital admissions rather than on individual patients, lacking crucial information about GCA disease severity, treatment regimens, medication adherence, and clinical outcomes following discharge.

The aim of this study is to analyze hospitalization rates, causes of hospitalization, and to identify potential risk factors related to the disease itself or its treatment. Understanding these factors is crucial for optimizing patient management,

improving quality of care, and reducing the risk of hospitalization and mortality in this vulnerable population.

1.6.2 METHODS

Patients were selected according to the following inclusion criteria, above mentioned for the "Study on Giant Cell Arteritis with Large Vessel Involvement and analysis of this specific disease subset": 1) patients with a new diagnosis of GCA made at Spedali Civili Brescia between January 1, 2005, and December 31, 2020, and meeting the 2022 ACR/EULAR classification criteria [59]; 2) complete medical history regarding disease onset; 3) a minimum follow-up of 6 months.

Clinical data for this study were collected during the first five years following the initial diagnosis of GCA. Information was obtained from both paper and electronic patient medical records, including demographic data, clinical features and disease activity, treatment regimens, and comorbidities. Hospitalizations that occurred at the time of diagnosis and admissions for day-hospital treatments were excluded from the analysis.

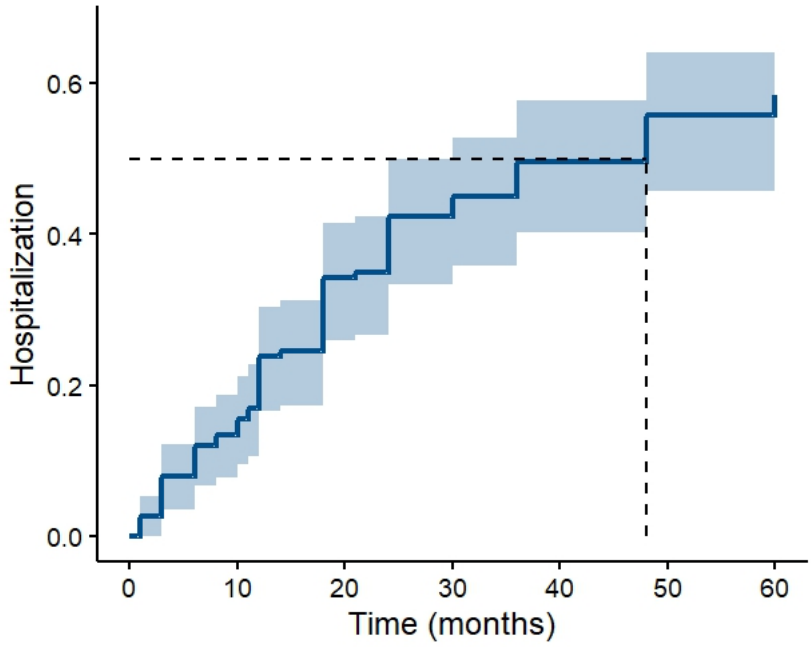
The statistical analysis began with the descriptive evaluation of variables, calculating the main indices of central tendency, expressed as median (1st-3rd interquartile), and percentage composition ratios. Differences between quantitative variables across patient groups were analyzed using the non-parametric Mann-Whitney test, while associations between nominal variables were assessed using the chi-square test or Fisher's exact test (if the expected frequency was <5). A p-value ≤ 0.05 was considered statistically significant. Survival and time to first hospitalization analysis was performed with Kaplan-Meier analysis (R Ecosystem).

1.6.3 RESULTS

We enrolled 150 patients with GCA, comprising 69% females and 31% males, with a median age at diagnosis of 73 years (IQR 67-78) and a median diagnostic latency of 5 weeks (IQR 3-12). Of these, 96 patients (63%) had cranial vasculitis (C-GCA), 22 (15%) had large-vessel vasculitis (LV-GCA), and 32 (22%) had both cranial and large vessels involvement. Regarding treatment, 52 patients (35%) received

glucocorticoids (GCs) alone, 52 (35%) were treated with GCs and tocilizumab (TCZ), and 46 (30%) with GCs and methotrexate (MTX).

A total of 74 patients (49%) experienced at least one hospitalization during the follow-up period, accounting for a total of 135 hospitalizations. Of the 74 patients, 43 had a single hospitalization, while 31 patients had two or more hospitalizations. The median time to first hospitalization was 48 months after diagnosis (Graph 1) and the mean hospitalization duration of 11 days per patient.



Graph 1. Kaplan-Meier curve for first hospitalization

A comparison was made between patients who had at least one hospitalization and those who were never hospitalized, analyzing demographic data, disease characteristics, and comorbidities at the time of diagnosis (Table 9 and 10). No significant differences were found regarding age at diagnosis or sex, nor in disease characteristics, particularly clinical phenotype (C, LV, LV-C), ocular involvement at onset, hospitalization at onset, or the use of immunosuppressants (MTX or TCZ). However, when comparing baseline comorbidities, smokers and hypertensive patients were found to be at higher risk of hospitalization during follow-up, as were patients with multiple comorbidities. In fact, patients hospitalized during follow-up had higher scores on the modified Rheumatic Disease Comorbidity Index (mRDCI) and the Charlson Comorbidity Index (CCI) at diagnosis [mRDCI 1 (1-2); CCI 4 (4-5)] compared to non-hospitalized patients [mRDCI 1 (0-1); CCI 4 (3-5)] (p mRDCI:

0.0043; p CCI: 0.0365). In the subsequent multivariate analysis mRDCI retained statistical significance (p: 0.0133).

Demographic	GCA (n: 150)	Hospitalization (n: 74)	NO hospitalization (n: 76)	p
Sex (F/M)	104 (69%)/46 (31%)	50 (68%)/24 (32%)	54 (71%)/22(29%)	0,6435
Age at diagnosis (years)	74 (67-78)	74 (68-78)	73 (67-78)	0,4223
Hospitalization at diagnosis	93 (62%)	43 (58%)	50 (66%)	0,3325
Ocular involvement	55 (37%)	27 (36%)	28 (37%)	0,9640
C-GCA	95 (63%)	47 (64%)	48 (63%)	0,9640
LV-GCA	22 (15%)	12 (16%)	10 (13%)	0,5966
LC-C-GCA	33 (22%)	15 (20%)	18 (24%)	0,6138
Immunosuppressant	99 (65%)	50 (68%)	49 (64%)	0,6892
MTX	44 (29%)	23 (31%)	21 (28%)	0,6427
TCZ	55 (37%)	27 (36%)	28 (37%)	0,9640

Table 9. Demographic characteristics and disease manifestations at diagnosis. Data expressed as *n* (%) or median (IQR)

Demographic	GCA (n: 150)	Hospitalization (n: 74)	NO hospitalization (n: 76)	p
Smoke	57 (38%)	34 (%)	23 (%)	0,0479
Obesity	14 (9%)	8 (%)	6 (%)	0,5393
Diabetes	16 (10%)	9 (%)	7 (%)	0,5582
Coronary heart disease	17 (11%)	8 (%)	9 (%)	0,8421
Hypertension	74 (49%)	43 (%)	31 (%)	0,0339
Cancer	19 (13%)	13 (%)	6 (%)	0,0749
Chronic kidney disease	5 (3%)	5 (%)	0 (%)	0,0212
Depression	8 (5%)	4 (%)	4 (%)	0,9691
Dyslipidemia	37 (25%)	18 (%)	19 (%)	0,9235
mRDCI at diagnosis	1 (0-2)	2 (1-3)	1 (1-2)	0,0043
CCI at diagnosis	4 (3-5)	5 (4-6)	4 (4-5)	0,0365

Table 10. Comorbidities at diagnosis. mRDCI: modified Rheumatic Disease Comorbidity Index: CCI: Charlson Comorbidity Index. Data expressed as *n* (%).

Analyzing hospitalizations causes, 6 hospitalizations were attributed to GCA relapses and 129 to other diseases.

The 6 hospitalizations for GCA relapse were characterized by temporal headache in three cases, visual impairment in one, polymyalgia rheumatica in one, severe anemia with jaw claudication in one case. These relapses occurred after a median time of 18 months (IQR 12-42) post-diagnosis. As treatment, glucocorticoid (GC) doses were increased in four cases, MTX was switched to tocilizumab TCZ in one case, and TCZ was added to GCs in another case.

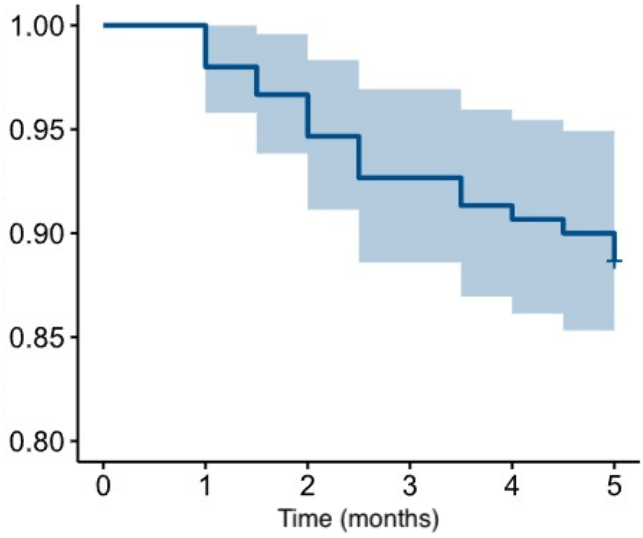
Of the remaining 129 hospitalizations, the most frequent causes were infections (29%), cardiovascular disease (25%), and surgeries (13%, with 9% being emergency procedures). The majority of patients were admitted to internal medicine wards (29%), followed by cardiology and cardiac surgery (18%), general and vascular surgery (15%), and orthopedics (10%). Additionally, 10 patients (8%) required admission to the intensive care unit (ICU). At the time of admission, 27 patients (21%) had active GCA. Analyzing ongoing therapy, 80 patients (61%) were on a daily GC dose of 10 mg or less, while 51 patients (39%) were on a higher dose. Immunosuppressive therapy was being administered in 61 cases (47%), including 35 on TCZ and 26 on MTX.

Among infections, the most commonly affected sites were the respiratory tract (36%), urinary tract (19%), sepsis (14%), gastrointestinal tract (12%), and skin (7%). The pathogenic microorganism was isolated in 71% of cases. Main infections were bacterial (80%), most of which caused by Escherichia coli (51%), except in the gastrointestinal tract, where the main pathogen was Clostridium difficile (50%), and in the respiratory tract. In fact, viral infections (12%) predominantly affected the respiratory tract, where they were primarily caused by SARS-CoV-2 (40%). Finally, fungal infections (7%) were mostly caused by Candida spp (Table 11).

Infection site	Number of isolated pathogens (n: 41)	Type of isolated pathogens
Respiratory tract	10/21 (48%)	SARS-CoV-2 (n: 4) Influenza A virus (n: 1) Chlamydia pneumoniae (n: 1) Klebsiella pneumoniae + Pseudomonas aeruginosa (n: 1) Heamophilus influenzae type b (n: 1) Candida albicans (n: 1) Candida glabrata + Pneumocystis jirovecii (n: 1)
Urinary tract	11/12 (92%)	Escherichia coli (n: 10) Proteus mirabilis (n: 1)
Sepsis	9/10 (90%)	Escherichia coli (n: 4) Pseudomonas aeruginosa (n: 2) Klebsiella oxytoca + Enterococcus faecium (n: 1) Enterococcus faecalis vancomycin-resistant (n: 1) Staphylococcus aureus methicillin-sensitive (n: 1)
Gastrointestinal tract	6/8 (75%)	Clostridium difficile (n: 3)
Skin	2/4 (50%)	Escherichia coli enteropathogenic (n: 1)
Central nervous system	1/1 (100%)	Campylobacter jejuni (n: 1)
Endocardium	1/1 (100%)	Candida albicans (n: 1)
Knee joint	1/1 (100%)	Escherichia coli (n: 1)

Table 11. Infections in hospitalized patients. Data expresses as n (%)

Seventeen patients (11%) died during follow-up period, with a median age at death of 83 (80-88) years and a median time from diagnosis to death of 30 months (IQR 18-42). Of these, eight patients (47%) died because of infections: seven due to pneumonia and one from peritonitis. Seven patients (41%) died of cancer, one of cardiac arrest, and one cause of death remained undetermined. Notably, only two patients died while hospitalized. The five-year survival probability for the cohort was 89% (95% CI: 84-94) (Graph 2).



Graph 2. Kaplan-Meier Kaplan-Meier survival curve

1.6.4 DISCUSSION

The aim of this study was to assess the risk of hospitalization in patients with GCA by analyzing a single-center cohort of 150 patients over the five years following diagnosis. Research on this topic is scarce, with all prior studies conducted in the United States, where the healthcare system, and consequently, hospitalization practices, differ significantly from Europe. To our knowledge, this is the first study on GCA hospitalizations conducted in Europe.

Our analysis revealed a high risk of hospitalization in GCA patients, with nearly half of the cohort experiencing at least one hospital admission during the follow-up period. This finding aligns with previous studies from the U.S., which also demonstrated that GCA patients are at higher risk of all-cause hospitalization compared to those without GCA.

Interestingly, disease characteristics at diagnosis, including severe manifestations like ocular involvement, were not associated with an increased risk of hospitalization. Similarly, neither sex nor age appeared to influence the risk of hospitalization, which contrasts with other studies that suggested female patients and those over 70 years of age were at higher risk. Instead, the most impactful factors were baseline comorbidities at the time of GCA diagnosis. Hospitalized patients had significantly higher scores on the modified rheumatic disease

comorbidity index (mRDCI) and the Charlson comorbidity index (CCI), indicating a greater burden of comorbid conditions.

In terms of specific comorbidities, smoking, hypertension, and chronic kidney disease were identified as significant risk factors for hospitalization during follow-up. These are well-established cardiovascular risk factors, which correlates with another important finding of our study: cardiovascular diseases were among the most frequent causes of hospitalization. Furthermore, the hospital units most frequently admitting GCA patients were cardiology and internal medicine, the latter being typically reserved for patients with multiple chronic conditions.

Infections were another major cause of hospitalization in both our cohort and those reported in U.S. studies. Moreover, infections emerged as the leading cause of death in our cohort. This is not surprising given that all GCA patients are treated with high doses of glucocorticoids, and 65% of patients in this study were also receiving concomitant immunosuppressive therapy.

On the other hand, the risk of hospitalization due to GCA relapse was relatively low. This could be attributed to the fact that relapses in these patients are often mild and managed on an outpatient basis rather than through hospital admissions.

Once again, our findings highlight that GCA patients should be considered a fragile population, not only due to the disease itself but also because of their advanced age, comorbidities, and the aggressive immunosuppressive treatments they require. This underscores the critical need for implementing comprehensive therapeutic and preventive measures aimed at managing comorbidities and preventing infections in this patient population.

A key strength of our study is the direct collection of clinical data from patient medical records, rather than relying solely on electronic registries and ICD codes. This allowed for more accurate identification of hospitalization causes, such as the specific types of infections, as well as a clearer understanding of disease status at the time of admission. Additionally, this is the first study of its kind conducted in Italy and Europe.

The main limitation of our study is the lack of a control group, as we were unable to compare the GCA cohort with the general population. Future studies will address this limitation by providing comparative data in a second phase of research.

1.6.5 CONCLUSION

Patients with GCA face a high risk of hospitalization, with approximately half of the patients in our cohort experiencing at least one hospital admission during the follow-up period. The main causes of hospitalization were infectious diseases and cardiovascular conditions. Notably, GCA disease characteristics at diagnosis, including severe manifestations such as ocular involvement, were not significantly associated with the risk of hospitalization. Instead, comorbidities like smoking, hypertension, and chronic kidney disease played a more substantial role in determining the likelihood of hospitalization.

In our cohort, GCA itself did not directly contribute to increased mortality, as no patient died from vasculitis. However, the use of immunosuppressive therapy may have had an impact, as the leading causes of death were infections and malignant neoplasms. This highlights the delicate balance between managing GCA and the potential risks of immunosuppressive treatments, especially in an elderly and comorbid population.

These findings emphasize the need for careful management of comorbid conditions and vigilant monitoring for infections to minimize hospitalization and improve outcomes in GCA patients. Understanding these factors is crucial for optimizing patient management, improving quality of care, and reducing the risk of hospitalization and mortality in this vulnerable population.

1.6.6 PUBLICATIONS ON THE TOPIC

1) Mora J, Regola F, Franceschini F, et al. AB1307 Prevalence and causes of hospitalization and mortality in Giant Cell Arteritis: analysis of a monocentric retrospective cohort of patients. Annals of the Rheumatic Diseases 2024;83:2001. https://doi.org/10.1136/annrheumdis-2024-eular.4095

AB1307

PREVALENCE AND CAUSES OF HOSPITALIZATION AND MORTALITY IN GIANT CELL ARTERITIS: ANALYSIS OF A MONOCENTRIC RETROSPECTIVE COHORT OF PATIENTS

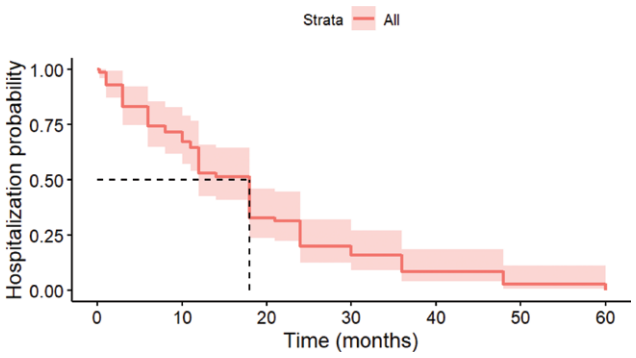
Keywords: Observational studies/ registry, Glucocorticoids, Epidemiology, Comorbidities, Real-world evidence

J. Mora[1], F. Regola[1], F. Franceschini[1], P. Toniati[2]. [1]*ASST Spedali Civili and University of Brescia, Rheumatology and Clinical Immunology, Brescia, Italy*; [2]*ASST Spedali Civili of Brescia, Rheumatology and Clinical Immunology, Brescia, Italy*

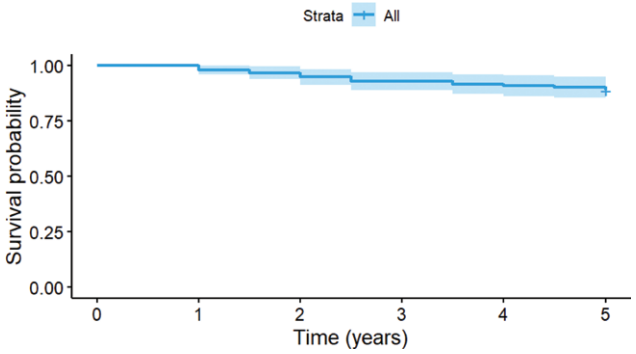
Background: Giant Cell Arteritis (GCA) is the most frequent vasculitis among people above the age of 50 years. GCA is associated with several irreversible outcomes, comorbidities, and treatment side effects, which can lead to hospitalization.
Objectives: The aim of this study was to analyze prevalence and causes of hospitalization and mortality in GCA patients during the first 5 years after diagnosis.
Methods: We analyzed a cohort of 150 patients meeting the 2022 ACR/EULAR criteria for GCA [1], diagnosed between 2003 and 2021 in our Center, and followed up for at least 6 months. Clinical data were collected in the first 5 years after diagnosis. Hospitalizations at diagnosis and day-hospital admissions were excluded. Statistical analysis was performed with Kaplan-Meier analysis (R Ecosystem).
Results: We enrolled 150 patients [F 69%; M 31%; median age at diagnosis 73 (IQR 67-78) years; diagnostic latency 6 (IQR 3-13) weeks] with GCA: 95 (63%) had cranial vasculitis (C-GCA), 22 (15%) large-vessel vasculitis (LV-GCA), and 33 (22%) both. Fifty-two (35%) patients were treated with glucocorticoids (GCs) alone, 52 (35%) with tocilizumab (TCZ), and 46 (30%) with methotrexate (MTX). Seventy-four patients (49%) had at least one hospitalization, with 43 having 1 [median time after diagnosis 18 months (95% CI: 12-18)] (Graph 1) and 31 having 2 or more. We recorded a total of 135 hospitalizations, with an average of about 2 hospitalizations per patient and 11 days of hospitalization length per patient. Patients hospitalized during follow-up had higher scores of the modified rheumatic disease comorbidity index (mRDCI) and the Charlson comorbidity index (CCI) at diagnosis [median mRDCI 1 (IQR 1-2); median CCI 4 (IQR 4-5)] compared to non-hospitalized patients [median mRDCI 1 (IQR 0-1); median CCI 4 (IQR 3-5)] (p mRDCI: 0,0043; p CCI: 0,0365). Six hospitalizations were caused by GCA relapse (3 for temporal headache, 1 for visual impairment, 1 for polymyalgia rheumatica, and 1 for anemia and masseter claudication), occurring after a median time after diagnosis of 18 (IQR 12-42) months. GCs were increased in 4 cases, MTX was changed to TCZ in 1 case, and TCZ was added to GCs in 1 case. In the remaining 129 cases, main causes of hospitalization were infectious diseases (29%), circulatory system diseases (25%) and surgery (13%, of which 9% emergency surgery). Among infections, main sites were respiratory tract (36%), urinary tract (19%), sepsis (14%), gastrointestinal tract (12%), and skin (7%). Most patients were admitted to internal medicine unit (29%), followed by cardiology and cardiac surgery units (18%), general surgery and vascular surgery units (15%), and orthopedics unit (10%). In addition, 10 patients (8%) were admitted to the intensive care unit. On admission, 27 patients (21%) had an active GCA and patients were taking a GC dose of 10 mg or lower in 80 cases (61%) and higher than 10 mg in 51 cases (39%), and an immunosuppressive therapy in 61 cases (47%), of which 35 TCZ and 26 MTX. Fifty-six irreversible GCA complications occurred in 47 patients (31%), including 29 (52%) visual impairment and 18 (32%) aortic aneurisms. Seventeen patients (11%) passed away during follow-up [median age 83 (IQR 80-88) years; median time after diagnosis 30 (IQR 18-42) months], 2 of whom during a hospital stay: 8 (47%) died of infection, of which 7 pneumonia and 1 peritonitis, 7 (41%) of cancer, 1 of cardiac arrest, and 1 undetermined. Survival probability was 89% (95% CI: 84-94) at 5 years (Graph 2).
Conclusion: Patients with GCA have a high risk of hospitalization occurring in about half of patients during follow-up. Infectious diseases and circulatory system diseases were the main causes of hospitalization. In our cohort, GCA itself did not contribute directly to increase mortality, as no patient died of vasculitis. Nevertheless, immunosuppressive therapy may have played a role, as the primary causes of death were infectious diseases and malignant neoplasms.

REFERENCES:

[1] Ponte C., et al. Arthritis Rheumatol. 2022. PMID: 36350123.



Graph 1. Kaplan-Meier curve for first hospitalization.



Graph 2. Kaplan-Meier survival curve.

Acknowledgements: NIL.
Disclosure of Interests: None declared.
DOI: 10.1136/annrheumdis-2024-eular.4095

1.7 STUDY ON GLUCOCORTICOID-RELATED ADVERSE EVENTS IN GIANT CELL ARTERITIS AND STEROID-SPARING EFFECT OF TOCILIZUMAB AND METHOTREXATE

1.7.1 AIM OF THE STUDY

The first-line therapy of GCA includes high doses of glucocorticoids (GC), with subsequent gradual tapering. However, more than 40% of patients experience relapses or a vascular disease progression during GC tapering, and more than 80% suffers from GC-related side effects. These side effects encompass diabetes mellitus, arterial hypertension, atherosclerosis or other cardiovascular diseases, infections, osteoporosis and neuropsychiatric manifestations. For these reasons, there is a pressing need for steroid-sparing agents and both the European League Against Rheumatism (EULAR) recommendations and the American College of Rheumatology (ACR) guidelines advocate for tocilizumab (TCZ) as the primary steroid-sparing agent to be used in this disease [47,60]. On the other hand, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate (MTX), have shown only partial steroid-sparing effect and clinical effectiveness, relegating them to a second-line therapy status [67].

TCZ, a humanized monoclonal antibody blocking interleukin (IL)-6 signaling, has demonstrated clinical efficacy and steroid-sparing effects in two randomized controlled trials (RCTs) [61,62]. However, due to the rarity of GCA and the recent approval of TCZ, only limited studies in the literature confirm its clinical efficacy, with no available studies addressing its steroid-sparing effect in real-word cohorts, different from those in the RCTs [65,66].

Recently, a multidisciplinary team developed the Glucocorticoid Toxicity Index (GTI) version 2.0 [111], an algorithm designed to quantify the GC-induced toxicity by assessing GC side effects and steroid-induced damage. Despite its validation in diseases such as ANCA-associated vasculitis and asthma, GTI 2.0 has not yet been validated for LVVs [112–114].

The aim of this study is presenting a analyzing the GC side effects in a large seal-life cohort and to quantify the GC-induced toxicity applying GTI 2.0. We also analyzed the steroid-sparing effect of TCZ and MTX in a real-word clinical setting.

1.7.2 METHODS

Patients were selected according to the following inclusion criteria, above mentioned for the "Study on Giant Cell Arteritis with Large Vessel Involvement and analysis of this specific disease subset": 1) patients with a new diagnosis of GCA made at Spedali Civili Brescia between January 1, 2005, and December 31, 2020, and meeting the 2022 ACR/EULAR classification criteria [59]; 2) complete medical history regarding disease onset; 3) a minimum follow-up of 6 months.
Clinical data for this study were collected during the first five years following the initial diagnosis of GCA. Information was obtained from both paper and electronic patient medical records, including demographic data, clinical features and disease activity, treatment regimens, and comorbidities.
Patients were classified according to the type of medical therapy administered. Patients were divided into 5 groups: GC (patients treated with GC alone), MTX-1 (patients treated with MTX introduced within 3 months after diagnosis), MTX-2 (patients treated with MTX introduced at least 3 months after diagnosis for GCA relapses or GC side effects), TCZ-1 (patients treated with TCZ introduced within 3 months after diagnosis), and TCZ-2 (patients treated with TCZ introduced at least 3 months after diagnosis for GCA relapses or GC side effects).
The GC-induced toxicity was assessed using the Glucocorticoid Toxicity Index (GTI) version 2.0 in order to classify GC-induced side effects and analyze the steroid-sparing effect of TCZ and MTX. GTI 2.0 is an algorithm developed by a multispecialty medical team, which allows to quantify the GC-induced toxicity. GTI 2.0 is composed by two sections that take into account all the possible GC side effects: the Composite Index and the Specific List. The Composite Index is composed by 9 domains representing main GC side effects, including variations in body mass index (BMI), glucose tolerance, blood pressure, lipid panel, GC-induced myopathy, bone mineral density (BMD), infections, GC-induced cutaneous toxicity and GC-induced neuropsychiatric side effects. The Composite Index is further

divided into two scores: the Cumulative Worsening Score (CWS), which represents the GC cumulative damage throughout the duration of the follow-up, and the Aggregate Improvement Score (AIS), that accounts the potential improvements between two timepoints, as some GC side effects are transient. The Specific List consists of 11 domains that address GC side effects not quantifiable by the Composite Index. For this reason, GC side effects listed in the Specific List are solely descriptive and are not suitable for statistical analysis. The minimal clinically important difference for the GTI scores is 10 [113]. In our study, we calculated both CWS and AIS assuming a baseline score of zero.

Disease activity and response to treatment were assessed by an expert rheumatologist at each timepoint. Patients were considered to be in remission if they exhibited no signs or symptoms of active GCA, and, when applicable, imaging revealed no evidence of disease activity. Relapses were defined as the recurrence of signs or symptoms of active GCA and/or, when applicable, imaging findings indicating disease activity. Major relapses were defined as relapses with severe symptoms or organ involvement, such as visual impairment, requiring high-dose GCs and adjustments to the immunosuppressive therapy strategy. Minor relapses were defined as episodes with mild symptoms, managed with short courses of low- to medium-dose GCs or minor adjustments in immunosuppressive therapy.

Data were presented as median (1st-3rd interquartile) or percentage composition for continuous and categorical variables, respectively. Fisher's exact test was employed to compare qualitative variables, while Mann-Whitney U test was used to compare continuous variables between groups. Variations from baseline to different timepoints were assessed using Wilcoxon's signed rank test for paired samples. Correlations were assessed with Pearson, Kendall or Spearman coefficient (according to variable type) to evaluate associations between variables. Statistical analysis was performed with either GraphPad statistical software package (GraphPad Software, Inc, CA, USA) or in R environment (R Core Team 2024) . A two-tailed P-value less than alpha reference of 0.05 was considered statistically significant. Multiple comparisons were assessed with post hoc tests.

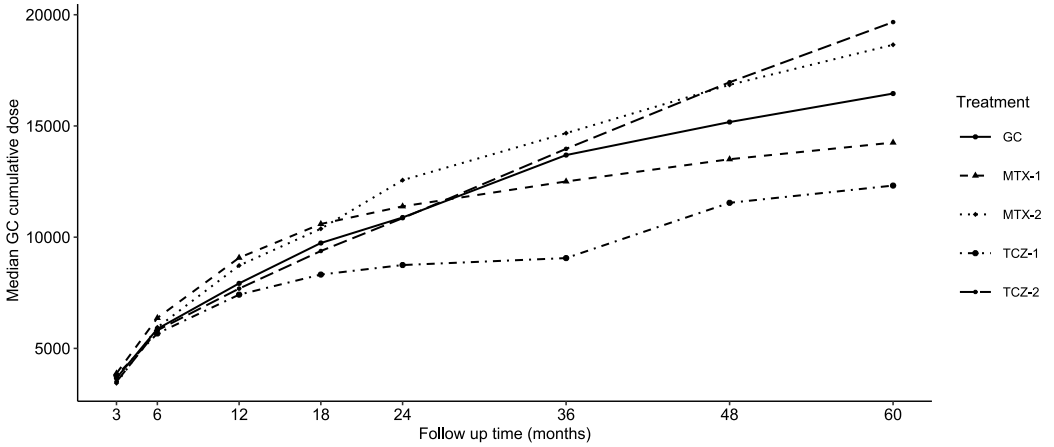
1.7.3 RESULTS

1.7.3.1 DEMOGRAPHIC AND CLINICAL FEATURES

One hundred fifty patients were enrolled in the study: 104 patients were females (69%) and 46 were males (31%) with a median age at diagnosis of 73 (67-78) years. Patients were categorized into three groups according to GCA clinical phenotype: 96 with C-GCA (64%), 22 with LV-GCA (15%), and 32 with C-LV-GCA (21%).
At diagnosis, 130 patients (87%) had at least one comorbidity, including arterial hypertension (74 patients, 49%), dyslipidemia (37 pts, 25%), malignant neoplasms (19 pts, 13%), cardiovascular diseases (17 pts, 11%), cataract (17 pts, 11%), diabetes mellitus (16 pts, 11%), obesity (14 pts, 9%), chronic lung diseases (11 pts, 7%), osteoporosis (10 pts, 7%), major depression (8 pts, 5%), peptic ulcer (5 pts, 3%), chronic renal failure (5 pts, 3%), and insufficiency fractures (1 pts, 1%). The mean of the modified rheumatic disease comorbidity index (mRDCI) was 1 (0-2) and the mean of the Charlson comorbidity index (CCI) was 4 (3-5).
Fifty-two patients (35%) were treated with glucocorticoids (GCs) alone, 20 (14%) with MTX-1, 26 (17%) with MTX-2, 26 (17%) with TCZ-1, and 26 (17%) with TCZ-2.

1.7.3.2 GC CUMULATIVE DOSE

Graphic 3 displays the temporal trend of the median GC cumulative dose in the different groups. Statistical analysis was performed comparing the groups of patients divided according to the type of medical therapy: GC vs TCZ-1, GC vs TCZ-2, GC vs MTX-1, GC vs MTX-2, TCZ-1 vs MTX-1.



Patients (n)	t3	t6	t12	t18	t24	t36	t48	t60
GC	52	52	49	40	35	25	19	17
MTX-1	20	20	17	17	16	13	13	9
MTX-2	26	26	25	23	21	20	19	17
TCZ-1	26	26	22	16	14	12	3	3
TCZ-2	26	26	25	23	21	16	13	12
Total	150	150	138	119	107	86	67	58

Graph 3. GC cumulative dose at different timepoints categorized by the type of medical therapy. Data are expressed as the median.

In comparing TCZ-1 patients with both GC and MTX-1 patients, a notable trend emerged, indicating a lower GC cumulative dose for TCZ-1 patients from the timepoint t24 onwards. Specifically, TCZ-1 patients accumulated a mean GC dose of 8319 (6961-9780) mg at t24 and 9060 (8326-11367) mg at t36, reflecting reductions of 23% (p: 0.0327) and 35% (p: 0.0222) respectively, compared to GC patients. Similarly, compared to MTX-1 patients, TCZ-1 patients showed reduction of 23% (p: 0.0323) and 26% (p: 0.0208) at the same timepoints. By t60, TCZ-1 patients had accumulated a mean GC dose of 12320 (12192-13259) mg, indicating reductions of 25% compared to GC patients and 13% compared to MTX-1 patients; however, these differences did not reach statistical significance. On the other hand, comparisons between GC vs TCZ-2 and GC vs MTX-2 did not show a statistically significant difference (Table 12).

	GC (n: 52)	MTX-1 (n: 20)	MTX-2 (n: 26)	TCZ-1 (n: 26)	TCZ-2 (n: 26)	p GC vs MTX-1	p GC vs MTX-2	p GC vs TCZ-1	p GC vs TCZ-2	p MTX-1 vs TCZ-1	p MTX-2 vs TCZ-2
t3	3664 (2526-4222)	3875 (3296-4098)	3436 (2067-4284)	3784 (3089-4145)	3499 (1809-4106)	0.8751	0.3564	0.5457	0.3620	0.7988	0.8049
t6	5876 (4289-7086)	6369 (5063-6990)	5944 (3467-7138)	5671 (4918-6991)	5811 (3811-7419)	0.5546	0.6035	0.9366	0.7829	0.5133	0.8620
t12	7923 (6313-9928)	9075 (7281-9868)	8725 (5736-10173)	7416 (6499-9089)	7689 (6255-11063)	0.4546	0.8981	0.4371	0.9772	0.1696	0.9175
t18	9738 (7639-12316)	10594 (8484-11363)	10379 (7756-12663)	8319 (6724-10343)	9378 (7941-14531)	0.6574	0.3133	0.2135	0.7040	0.1089	0.7576
t24	10885 (8664-13472)	11386 (9150-12529)	12563 (8565-14556)	8747 (6961-9780)	10854 (9531-18910)	0.9272	0.3697	0.0327	0.5881	0.0323	0.9900
t36	13691 (10229-16345)	12505 (10689-14103)	14676 (10642-16908)	9060 (8326-11367)	13971 (10696-20353)	0.7818	0.3792	0.0222	0.6210	0.0208	0.9113
t48	15176 (11510-19424)	13504 (11859-15763)	16848 (12629-20370)	11545 (11023-12871)	16965 (11363-20590)	0.3866	0.5838	0.1571	0.6451	0.3463	0.9694
t60	16457 (13218-21001)	14253 (13218-20703)	18650 (13065-21761)	12320 (12193-13259)	19670 (12232-23801)	0.6276	0.6543	0.0903	0.6740	0.2091	0.7398

Table 12. GC cumulative dose at different timepoints categorized by the type of medical therapy. Data are expressed as the median (1st-3rd interquartile).

1.7.3.3 GC SIDE EFFECTS

Throughout the follow-up period, GC side effects were observed in 132 patients (88%). A total of 451 GC-related side effects were documented with an average occurrence of about 3.4 GC-related side effects per patient. Notably, 369 (82%) side effects occurred within the initial 2 years following diagnosis and the initiation of GC treatment.

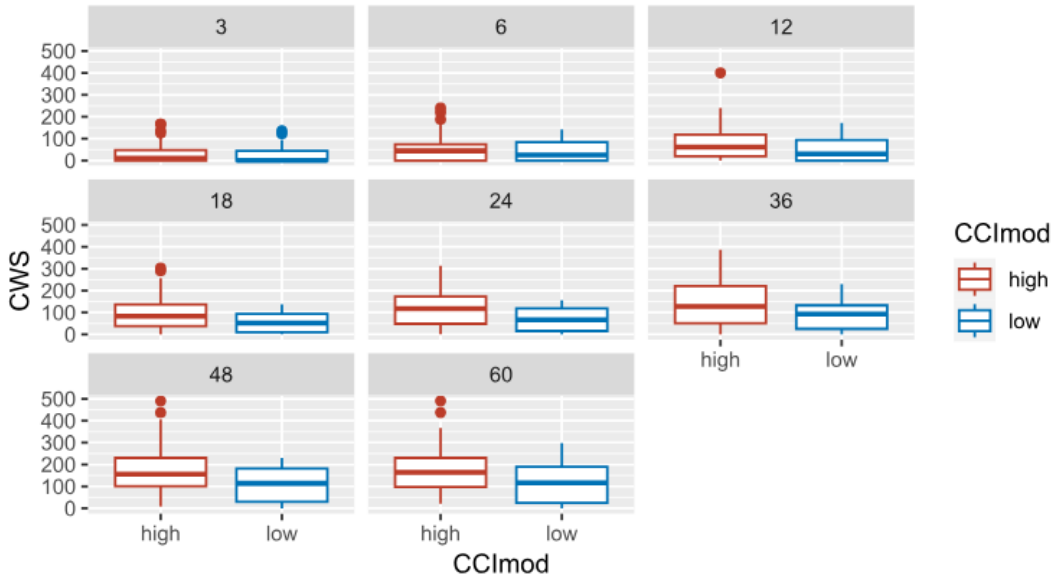
The most prevalent GC side effects included arterial hypertension (14%) and infections (14%), followed by neuropsychiatric manifestations (12%), diabetes mellitus (9%), cataract (8%), dyslipidemia (8%), cardiovascular diseases other than arterial hypertension (6%), weight gain (6%), osteoporosis (6%), GC-induced myopathy (4%), insufficiency fractures (4%), Cushingoid features (1%), glaucoma (1%), avascular necrosis (< 1%), tendon rupture (< 1%), and gastrointestinal symptoms (< 1%). Among infections, urinary tract infections (UTIs) were the most common (20%), followed by pneumonias (11%), acute bronchitis (7%), and herpes zoster (6%). Reported cardiovascular diseases, other than arterial hypertension, included deep venous thrombosis (35%), atrial fibrillation (23%), acute heart failure (15%), acute myocardial infarction (15%), and stroke or TIA (12%).

1.7.3.4 GC SIDE EFFECTS: CORRELATIONS WITH COMORBIDITIES AND GC CUMULATIVE DOSE

With the aim of identifying potential factors determining the increased risk of developing GC-related side effects, excluding the possible effect of

immunosuppressive drugs (analyzed in the next section), an analysis of the overall cohort was conducted using the GTI 2.0, calculated using the two Composite Index scores, CWS and AIS.

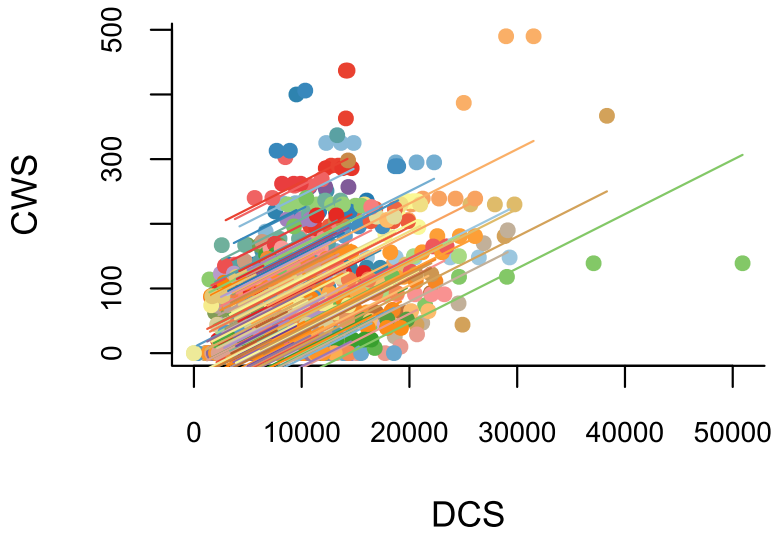
Firstly, to investigate potential correlations between comorbidities at diagnosis and the development of GC-induced side effects, a correlation analysis was performed between GTI 2.0 CWS and disease comorbidity indexes (CCI and mRDCI) at the time of diagnosis. No statistically significant correlation emerged between mRDCI at baseline and CWS at different timepoints. In the correlation analysis between the baseline CCI and CWS at various timepoints, a baseline CCI value ≤ 3 was categorized as low (low CCI), while a baseline CCI value > 3 was categorized as high (high CCI). Patients with a high CCI at baseline exhibited significantly higher CWS scores during the follow-up period. Specifically, the difference was statistically significant from timepoint t18 (p:0.021) to timepoint t48 (p:0.026) and showed a trend toward statistical significance at timepoint t60 (p:0.061) (Graph 4).



Graph 4. Correlation analysis between GTI 2.0 CWS and CCI at diagnosis. A baseline CCI value ≤ 3 was categorized as low (low CCI), while a baseline CCI value > 3 was categorized as high (high CCI).

Secondly, to analyze the potential correlations between GC cumulative dose and the development of GC-induced side effects, a correlation analysis was performed between GC cumulative dose and GTI 2.0 at different timepoints. This analysis

revealed a positive correlation between the GC cumulative dose and GTI 2.0 CWS when accounted for repeated measures ($p < 0.0001$) [115] (Graph 5).



Graph 5. Correlation analysis between GC cumulative dose and GTI 2.0 CWS when accounted for repeated measures.

1.7.3.5 TCZ AND MTX EFFECTS ON GC SIDE EFFECTS

Statistical analysis was conducted to compare patient groups categorized by the type of medical therapy: GC vs MTX-1, GC vs MTX-2, GC vs TCZ-1, GC vs TCZ-2, MTX-1 vs TCZ-1, and MTX-2 vs TCZ-2 (Table 13).

Side effects	Cohort (n: 150)	GC (n: 52)	MTX-1 (n: 20)	MTX-2 (n: 26)	TCZ-1 (n: 26)	TCZ-2 (n: 26)	p
Infections	64 (43%)	26 (50%)	9 (45%)	10 (38%)	5 (19%)	14 (54%)	0.0736
Hypertension	63 (42%)	23 (44%)	12 (60%)	11 (42%)	7 (27%)	10 (38%)	0.2553
Neuropsychiatric manifestations	53 (35%)	23 (44%)	12 (60%)	9 (35%)	3 (11%)	6 (23%)	0.0040
Diabetes mellitus	42 (28%)	15 (29%)	8 (40%)	6 (23%)	7 (27%)	6 (23%)	0.7197
Cataract	38 (25%)	15 (29%)	3 (15%)	10 (38%)	5 (19%)	5 (19%)	0.3019
Dyslipidemia	37 (25%)	13 (25%)	8 (40%)	5 (19%)	2 (8%)	9 (35%)	0.0791
Dermatologic manifestations	29 (19%)	9 (17%)	7 (35%)	6 (23%)	3 (11%)	4 (15%)	0.3094
Cardiovascular diseases	26 (17%)	12 (23%)	2 (10%)	6 (23%)	2 (8%)	4 (15%)	0.3667
Weight gain	25 (17%)	11 (21%)	5 (25%)	4 (15%)	3 (11%)	2 (8%)	0.4395
Osteoporosis	25 (17%)	6 (11%)	3 (15%)	8 (31%)	3 (11%)	5 (19%)	0.2520
GC-induced myopathy	19 (13%)	6 (11%)	4 (20%)	4 (15%)	1 (4%)	4 (15%)	0.5236
Cushingoid features	6 (4%)	1 (2%)	1 (5%)	1 (4%)	1 (4%)	2 (8%)	0.8155
Glaucoma	4 (3%)	3 (6%)	0	1 (4%)	0	0	0.4006
Avascular necrosis	2 (1%)	0	0	1 (4%)	0	1 (4%)	0.4309
Tendon rupture	1 (< 1%)	1 (2%)	0	0	0	0	0.7546
Gastrointestinal symptoms	1 (< 1%)	0	0	0	0	1 (4%)	0.3083
Total GC side effects	451	169	74	86	43	79	N/A
Side effects per patient (mean)	3.4	3.6	3.9	3.3	2.5	3.4	N/A
Patients with ≥ 1 side effect	132 (88%)	47 (90%)	19 (95%)	26 (100%)	17 (65%)	23 (88%)	0.0017
Patients with ≥ 3 side effects	67 (45%)	23 (44%)	14 (70%)	12 (46%)	5 (19%)	13 (50%)	0.015

Table 13. GC side effects categorized by the type of medical therapy. Data are expressed as n (%) or mean.

Examination of GC side effect incidence revealed a notable discrepancy across patient groups, indicating a higher prevalence of patients experiencing at least one side effect in the GC (90%), MTX-1 (95%), MTX-2 (100%), and TCZ-2 (88%) groups compared to TCZ-1 group (65%) (p: 0.0017). Furthermore, patients in the first four groups reported a higher number of GC side effects per patient compared to TCZ-1 patients: patients with ≥ 3 GC side effects were 44% in the GC group,

70% in MTX-1, 46% in MTX-2, and 50% in TCZ-2 compared to 19% in the TCZ-1 group (p: 0.0151).

The comparison between patients treated with immunosuppressants introduced at least 3 months after diagnosis (TCZ-2 and MTX-2) showed that only 30% of TCZ-2 patients experienced GC side effects after the introduction of TCZ, compared to 70% who developed them before starting the therapy ($p < 0.0001$). In contrast, 45% of MTX-2 patients developed GC side effects after the introduction of MTX, compared to 55% who developed them before the therapy (p: 0.2225).

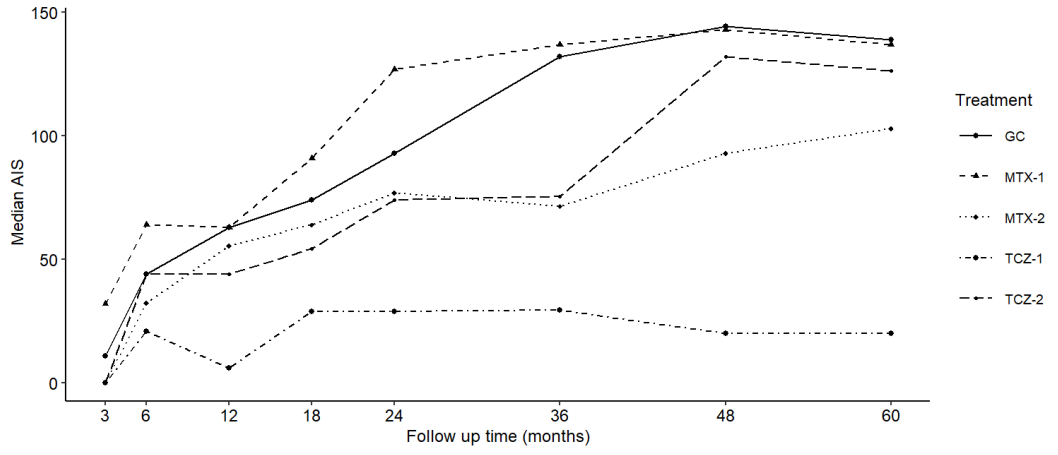
Further comparison of specific GC side effect incidence in different groups showed statistically significant differences, particularly in the occurrences of infections, lower in TCZ-1 group compared to GC (19% vs 50%; p: 0.0134), arterial hypertension, lower in TCZ-1 group compared to MTX-1 group (27% vs 60%; p: 0.0355), dyslipidemia, lower in TCZ-1 group compared to MTX-1 group (8% vs 40%; p: 0.0125), and in neuropsychiatric GC side effects, lower in TCZ-1 group compared to GC (11% vs 44%; p: 0.0047) and to MTX-1 (11% vs 60%; p: 0.0011).

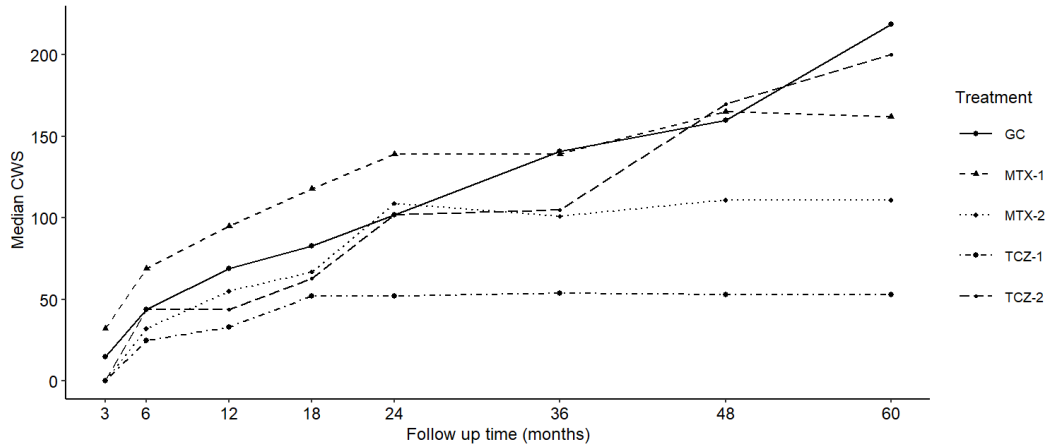
1.7.3.6 TCZ AND MTX EFFECTS ON GC SIDE EFFECTS: APPLICATION OF GTI 2.0

Graphic 6 displays the temporal trend of the GTI 2.0, calculated using the two Composite Index scores, AIS and CWS, in relation to the type of medical therapy administered to patients (GC, MTX-1, MTX-2, TCZ-1, and TCZ-2).

Regarding GTI 2.0 AIS, comparing TCZ-1 patients to GC patients and to MTX-1 patients, a trend to statistical significance was showed, with lower scores in TCZ-1 group. In particular, there was a difference of 52%, 90%, 61%, 69%, 78%, 86%, and 86% for TCZ-1 patients vs GC patients, and a difference of 67%, 90%, 68%, 77%, 79%, 86%, and 85% for TCZ-1 patients vs MTX-1 patients, respectively at timepoints t6, t12, t18, t24, t36, t48, and t60.

In the same way, GTI 2.0 CWS between TCZ-1 patients and GC patients or MTX-1 patients presented a trend to statistical significance, showing a difference of 43%, 51%, 38%, 49%, 62%, 67%, and 76% for TCZ-1 patients vs GC patients, and a difference of 64%, 65%, 56%, 63%, 61%, 68%, and 67% for TCZ-1 patients vs MTX-1 patients, respectively at timepoints t6, t12, t18, t24, t36, t48, and t60.





Patients (n)	t3	t6	t12	t18	t24	t36	t48	t60
GC	52	52	49	40	35	25	19	17
MTX-1	20	20	17	17	16	13	13	9
MTX-2	26	26	25	23	21	20	19	17
TCZ-1	26	26	22	16	14	12	3	3
TCZ-2	26	26	25	23	21	16	13	12
Total	150	150	138	119	107	86	67	58

Graph 5. GTI 2.0 AIS and CWS at different timepoints categorized by the type of medical therapy. Data are expressed as the median.

1.7.3.7 ANALYSIS OF RELAPSES AND IRREVERSIBLE GCA COMPLICATIONS

Within the entire cohort, 63 patients (42%) experienced a relapse of GCA accounting for a total of 94 relapses, of which 54 classified as minor (57%) and 40 as major (43%), and an average of 1.5 relapses per patient. Dividing the cohort based on therapy, 20 GC patients developed 26 relapses (38%), of which 8 major and 18 minor, 9 MTX-1 patients 15 relapses (45%), of which 5 major and 10 minor,

19 MTX-2 patients 28 relapses (73%), of which 13 major and 15 minor, TCZ-1 patients none, and 15 TCZ-2 patients 25 relapses (58%), of which 14 major and 11 minor. Statistical analysis revealed a significant difference for both the proportion of patients who relapsed ($p < 0.0001$) and the absolute number of relapses ($p < 0.0001$). Specifically, significant differences were observed between GC and TCZ-1 ($p < 0.0001$ and $p < 0.0001$, respectively) and MTZ-1 vs TCZ-1 (p: 0.0002 and $p < 0.0001$, respectively). Furthermore, only 4 TCZ-2 patients (16%) developed a minor relapse after initiation of TCZ compared to 12 MTX-2 patients (43%) after initiation of MTX, of which 7 experienced major relapses (p: 0.0410).

In the entire cohort, 46 patients (31%) had at least an irreversible GCA complication with a total of 51 GCA complications: visual impairment (57%), aortic ectasia or aneurism (33%), stroke (6%), chronic lower limb claudication (2%), and chronic upper limb claudication (2%). GC patients developed 22 complications (43%), MTX-1 patients 3 (6%), MTX-2 patients 9 (18%), TCZ-1 patients 6 (12%), and TCZ-2 patients 11 (21%). A statistically significant difference between GC group and other groups was observed (GC vs MTX-1 $p < 0.0001$, GC vs MTX-2 p: 0.0092, GC vs TCZ-1 p: 0.0007, and GC vs TCZ-2 p: 0.0335), especially in relation to the visual impairment (GC vs MTX-1 p: 0.0008, GC vs MTX-2 p: 0.0239, GC vs TCZ-1 p: 0.0096, and GC vs TCZ-2 p: 0.0096). Comparisons between other groups (MTX-1 vs TCZ-1 and MTX-2 vs TCZ-2) and according to the other types of GCA complications did not show a statistically significant difference.

1.7.4 DISCUSSION

The treatment of GCA relies on the use of high-dose GCs. However, despite GC treatment, approximately 40% of patients experience a disease relapse and the chronic use of GCs is associated with an incidence of over 80% of side effects, affecting prognosis. For these reasons, in recent years, significant attention has been paid to the potential use of immunosuppressive drugs in combination with GCs, particularly MTX and TCZ.

The aim of this study was to analyze the side effects of GCs in a well-characterized cohort of patients with GCA, examining their incidence and progression over time, and quantifying the overall damage induced by GCs through the application of the

GTI 2.0 [111]. The second part of the study aimed to demonstrate the potential steroid-sparing effect of TCZ and MTX.

The analysis of the historical cohort of GCA patients from our center allowed the identification of 150 patients with GCA, well-characterized from clinical, laboratory, and instrumental perspectives.

The cumulative dose of GCs for the entire cohort was 7,923 mg after 1 year from diagnosis and 16,457 mg after 5 years. This cumulative dose was higher compared to RCT trials but aligned with the few data available in the literature [61,79]. The difference between the cumulative dose in RCT trials and real-life settings is likely secondary to the different therapeutic approaches in pharmacological trials compared to the outpatient setting, where the GC tapering protocol is not standardized but reflects a more personalized approach based on disease activity and clinical characteristics of each patient.

Chronic GC therapy is recognized as a risk factor for numerous diseases, such as diabetes mellitus, hypertension, atherosclerosis, cardiovascular diseases, infections, and osteoporosis, and for most of these side effects, a dose-dependent effect of the cumulative GC dose has been demonstrated [69]. To confirm this observation and to calculate the cumulative damage induced by GCs in GCA, we calculated the incidence of each side effect and the GTI 2.0 score at different follow-up times.

During the follow-up, approximately 9 out of 10 patients in our cohort developed at least one side effect secondary to GC therapy, with an average of 3.4 events per patient. The most frequent GC side effects were arterial hypertension and infections. The increased risk of severe infections (grade ≥ 3 according to GTI 2.0) observed in this study was an expected finding due to the immunosuppressive effect of steroid therapy, and it aligns with previously published data. In fact, a recent retrospective study conducted in France highlighted a high risk of severe infections in the first year after GCA diagnosis, especially in patients with greater exposure to chronic GC therapy [71]. Neuropsychiatric side effects, such as anxiety, insomnia, and depression, were also frequently reported in our cohort and, in one case, were complicated by GC-induced acute psychosis. It is noteworthy that the high incidence of these side effects in the cohort could be partially due to the emotional

impact associated with the GCA diagnosis itself, particularly if associated with visual complications at disease onset, and not entirely attributable to GC effects.

To identify potential factors determining the increased risk of developing GC-related side effects, we analyzed the role of comorbidities at diagnosis and the possible dose-dependent effect of GC-induced damage. Specifically, a positive correlation between a high CCI (CCI > 3), a comorbidity index, and the GTI 2.0 CWS was demonstrated in the entire cohort, supporting the hypothesis that patients with more baseline comorbidities are at increased risk of developing new comorbidities or experiencing worsening of pre-existing ones. Subsequently, also the relationship between GTI 2.0 and GC cumulative dose was analyzed and a positive correlation was demonstrated between these parameters.

The second part of the study aimed to demonstrate the potential steroid-sparing effect of TCZ and MTX and their efficacy. Regarding MTX, to date, there are no RCT studies in the literature on its efficacy in GCA. Conversely, in 2017, TCZ demonstrated its efficacy in two RCT studies [61,62]. In total, 170 GCA patients were treated in these studies and TCZ demonstrated superior efficacy to placebo in inducing and maintaining disease remission after 52 weeks of treatment in both studies. Additionally, TCZ showed a steroid-sparing effect, allowing a reduction in the cumulative GC dose in patients treated with TCZ compared to those in the placebo groups. Given the rarity of the disease and the recent approval of the drug, few studies in the literature have examined the use of TCZ in real-life cohorts of GCA patients, which seem to confirm the efficacy of TCZ on disease activity. However, there are no published studies on the steroid-sparing effect of TCZ in cohorts other than those from the two RCTs.

Our cohort analysis confirmed the steroid-sparing effect of TCZ when used as first-line therapy and started at diagnosis or within 3 months after diagnosis (TCZ-1). Specifically, patients in the TCZ-1 group accumulated 25% less GC cumulative dose compared to patients treated only with GCs. Conversely, no significant differences were observed in the comparison between patients treated with GC drugs and those treated with MTX (MTX-1 and MTX-2) and second-line TCZ (TCZ-2). The lower cumulative GC dose in the TCZ-1 group was also associated with fewer GC side effects and less cumulative GC-induced damage. In fact, in the

GC group, 90% of patients developed at least one side effect, but this percentage decreased to 65% in the TCZ-1 group. Additionally, in the GC group, 44% of patients developed at least three side effects with a mean of 3.6 GC side effects per patient, compared to 19% in the TCZ-1 group and a mean of 2.5 GC side effects per patient in the TCZ-1 group. These data suggest that first-line TCZ reduces the incidence of GC-induced side effects and the number of GC side effects per patient. This result is also supported by the analysis of GTI 2.0 progression over time in the different groups. Both the GTI 2.0 AIS, an index of the active damage at the time of examination, and the GTI 2.0 CWS, an index of the cumulative patient damage, were lower in the TCZ-1 group compared to the GC group, with a difference of 86% and 67%, respectively.

Conversely, the effect of MTX was significantly lower, both in terms of the GC cumulative dose and the incidence of GC side effects, as well as in the calculation of the cumulative GC-induced damage. These data align with previous retrospective studies and meta-analyses on MTX, in which the drug showed only a modest steroid-sparing effect [67].

In addition to the steroid-sparing effect of TCZ, its clinical efficacy in inducing disease remission and reducing the number of disease relapses and short- and long-term disease outcomes was also analyzed. In the entire cohort of 150 patients, about 40% of the patients had at least one disease relapse, but none occurred in the TCZ-1 group. Similarly, in the TCZ-2 group, which included patients who started TCZ following a disease relapse or after developing GC-induced side effects, only 16% of patients experienced a relapse after starting TCZ. Therefore, these data confirm the efficacy of TCZ in inducing and maintaining disease remission, whether used as first-line or second-line treatment. On the contrary, MTX did not demonstrated any efficacy in reducing the number of disease relapses. Similarly, the analysis of disease outcome incidence showed a difference depending on the therapy used, demonstrating that GC monotherapy was associated with a higher incidence of disease complications compared to combination therapy with MTX or TCZ.

Regarding the limitations of this study, the retrospective design is a primary one. The GTI 2.0 score was designed for application in RCT studies, with prospective data collection, although it is also applicable to retrospective cohorts, as in our

study. However, as expected in retrospective studies, the presence of missing data can reduce the uniformity of collected data and their statistical significance. To mitigate biases related to this limitation, the inclusion criteria was the presence of complete clinical follow-up data for at least 6 months.

On the contrary, some of the strengths of this study include the large sample size, the uniformity of the collected data due to it being a single-center cohort, and the long duration of follow-up. Regarding the latter point, in the literature, the GTI 2.0 score has been validated for bronchial asthma and ANCA-associated vasculitis [112–114], analyzing the variation of this parameter over a 1-year period. To our knowledge, this study represents the first instance where the GTI 2.0 has been applied in a cohort followed longitudinally for more than 12 months.

1.7.5 CONCLUSION

In our cohort of 150 patients with GCA, it was confirmed that chronic use of GCs is associated with a high incidence of side effects, developed in approximately 90% of patients. Furthermore, GC-induced damage was found to be correlated with the GC cumulative dose and the presence of comorbidities at the time of diagnosis. Based on these data, the need to identify immunosuppressive drugs to treat GCA patients becomes evident, ensuring therapeutic efficacy while simultaneously reducing the GC dose. TCZ has demonstrated clinical efficacy and steroid-sparing effect in highly selected cohorts of patients within two RCT studies. In this study, for the first time, its steroid-sparing effect has been demonstrated in a cohort reflecting real clinical practice. In our study, patients treated with TCZ as first-line therapy (TCZ-1) accumulated 25% less GC cumulative dose compared to patients treated with GCs alone. This reduction in GC cumulative dose was associated with a lower incidence of GC-related side effects and less damage, as quantified by the GTI 2.0 score. Moreover, TCZ also demonstrated its efficacy in inducing and maintaining remission in patients when treated early in the course of the disease (TCZ-1 group). Similar efficacy was demonstrated among patients who initiated TCZ as second-line therapy, following disease relapse or after developing GC-induced adverse events (TCZ-2 group): in this group as well, the number of patients

experiencing disease relapse during TCZ therapy was lower than in the control group treated with GCs alone.

In conclusion, GCs represent a cornerstone in GCA therapy, but they are associated with a high incidence of side effects, and their cumulative dose correlates with induced damage, as quantified by the new GTI 2.0 score. TCZ has reaffirmed its status as a valid therapeutic option in a real-life cohort, allowing for a reduction in GC cumulative dose and consequently reducing their side effects.

1.7.6 PUBLICATIONS ON THE TOPIC

1) Regola F, Mora J, Bosio G, et alPOS0805 Glucocorticoid-related adverse events in Giant Cell Arteritis: application of the Glucocorticoid Toxicity Index in a monocentric cohort of 140 patients. Annals of the Rheumatic Diseases 2022;81:692. https://doi.org/10.1136/annrheumdis-2022-eular.2828

2) Regola F, Mora J, Bosio G, Andreoli L, Franceschini F, Toniati P. Glucocorticoid-related Adverse Events in Giant Cell Arteritis: Application of the Glucocorticoid Toxicity Index in a Monocentric Cohort of 140 Patients. Arthritis Rheumatol. 2022; 74 (suppl 9). https://acrabstracts.org/abstract/glucocorticoid-related-adverse-events-in-giant-cell-arteritis-application-of-the-glucocorticoid-toxicity-index-in-a-monocentric-cohort-of-140-patients/.

POS0805

GLUCOCORTICOID-RELATED ADVERSE EVENTS IN GIANT CELL ARTERITIS: APPLICATION OF THE GLUCOCORTICOID TOXICITY INDEX IN A MONOCENTRIC COHORT OF 140 PATIENTS

F. Regola[1,2], J. Mora[1], G. Bosio[3], L. Andreoli[1,2], F. Franceschini[1,2], P. Toniati[2].
[1]University of Brescia, Department of Clinical and Experimental Sciences, Brescia, Italy; [2]ASST-Spedali Civili of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy; [3]ASST-Spedali Civili of Brescia, Nuclar Medicine Unit, Brescia, Italy

Background: Oral glucocorticoids (GC) are the mainstay of treatment for giant cell arteritis (GCA) but chronic exposure to GC is associated with serious comorbidities.

Objectives: The objective of this study was to determine the GC exposure and risk of GC-related adverse events (AEs) in GCA, validating the Glucocorticoid Toxicity Index (GTI) (1,2) in a cohort of real-world patients.

Methods: 140 consecutive patients with GCA were enrolled in this retrospective monocentric study. All patients were older than 50 years of age, met the 1990 ACR criteria for GCA and/or had the evidence of a large vessel vasculitis at FDG-PET/CT scan. Patients' clinical data were collected from clinical charts, calculating GC cumulative dose and GTI at baseline and in the following 5 years.

Results: 140 patients were enrolled in the study: median (IQR) age at diagnosis 74 (67-79), Female: 97 (69%), Male: 43 (31%). According to vascular involvement patients were classified in cranial-GCA (C-GCA, n:91), large vessel-GCA (LV-GCA, n:21) and cranial and large vessel-GCA (LV-C-GCA, n:28). Furthermore, 50 (36%) patients were treated with only GC, 44 (31%) with GC+methotrexate (MTX), 46 (33%) with GC+tocilizumab (in 20 cases TCZ was started in the first 3 months after diagnosis: early-TCZ, in 26 cases after 3 months for relapses or AEs: late-TCZ).

During the follow up, 57 (41%) patients presented at least one relapse. In the GC group 22 relapses in 18 patients were reported, in MTX group 33 relapses in 25 patients (with 15 relapses before and 18 after MTX start), in early-TCZ group no relapses were reported, in late-TCZ group 21 relapses in 14 patients (with 17 relapses before and 4 after TCZ start) were reported.

Median cumulative GC doses after 1 and 5 years were respectively 7.9 (6.3-9.8) gr and 16.5 (13.8-18.9) gr in GC group, 8.7 (5.9-10.0) gr and 16.5 (13.2-20.7) gr in MTX group, 7.1 (5.5-8.0) gr and 13.3 (12.8-13.7) gr in early-TCZ and 7.7 (6.2-11.1) gr and 19.7 (12.2-23.8) gr in late-TCZ. Eighty-eight percent of patients developed at least one GC-AE, with infections and hypertension being the most common reported AEs (42% e 44%, respectively). Median GTI-CWS (Cumulative Worsening Score) after 1 year was 65 (20-137) in GC, 63 (10-95) in MTX, 51 (33-116) in TCZ-early, 44 (0-91) in TCZ-late. Median GTI-CWS after 5 years was 219 (118-240) in GC, 137 (65-206) in MTX, 147 (146-147) in TCZ-early, 200 (121-231) in TCZ-late. A correlation between GTI-CWS and the GC cumulative dose was found (after 5 years r: 0.295, p: 0.026).

Conclusion: Chronic GC treatment is associated with a high risk of developing comorbidities. GTI score demonstrated to be an effective tool to assess GC-related AEs and proved to correlate with GC cumulative dose. TCZ confirmed its efficacy in reducing relapse rate, both in early and late-TCZ groups (3). TCZ showed for the first time in a real-life cohort a GC sparing effect, with a 19% reduction in GC cumulative dose and a 33% reduction in GTI-CWS in 5 years (comparing GC group *vs* early-TCZ group).

REFERENCES:

[1] Glucocorticoid Toxicity Index (Copyright © 2016, 2018. Massachusetts General Hospital. All rights reserved.)
[2] Miloslavsky EM et al. Ann Rheum Dis. 2017 doi: 10.1136/annrheumdis-2016-210002.
[3] Stone JH et al. N Engl J Med. 2017 doi: 10.1056/NEJMoa1613849.

Disclosure of Interests: None declared

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ABSTRACT NUMBER: 0481

Glucocorticoid-related Adverse Events in Giant Cell Arteritis: Application of the Glucocorticoid Toxicity Index in a Monocentric Cohort of 140 Patients

Francesca Regola[1], Jacopo Mora[1], Giovanni Bosio[2], Laura Andreoli[1], Franco Franceschini[1] and Paola Toniati[1], [1]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili and University of Brescia, Brescia, Italy, [2]Nuclear Medicine Unit, ASST Spedali Civili of Brescia, Brescia, Italy

Meeting: ACR Convergence 2022

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SESSION INFORMATION

Date: Saturday, November 12, 2022

Session Type: Poster Session A

Title: Vasculitis – Non-ANCA-Associated and Related Disorders Poster I: Giant Cell Arteritis

Session Time: 1:00PM-3:00PM

Background/Purpose: Oral glucocorticoids (GC) are the mainstay of treatment for giant cell arteritis (GCA) but chronic exposure to GC is associated with serious comorbidities. The objective of this study was to determine the GC exposure and risk of GC-related adverse events (AEs) in GCA, validating the Glucocorticoid Toxicity Index (GTI) (1,2) in a cohort of real-world patients.

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Results: 140 patients were enrolled in the study: median (IQR) age at diagnosis 74 (67-79), Female: 97 (69%), Male: 43 (31%). According to vascular involvement patients were classified in cranial-GCA (C-GCA, n:91), large vessel-GCA (LV-GCA, n:21) and cranial and large vessel-GCA (LV-C-GCA, n:28). Furthermore, 50 (36%) patients were treated with only GC, 44 (31%) with GC+methotrexate (MTX), 46 (33%) with GC+tocilizumab (in 20 cases TCZ was started in the first 3 months after diagnosis: early-TCZ, in 26 cases after 3 months for relapses or AEs: late-TCZ).

During the follow up, 57 (41%) patients presented at least one relapse. In the GC group 22 relapses in 18 patients were reported, in MTX group 33 relapses in 25 patients (with 15 relapses before and 18 after MTX start), in early-TCZ group no relapses were reported, in late-TCZ group 21 relapses in 14 patients (with 17 relapses before and 4 after TCZ start) were reported.

Median cumulative GC doses after 1 and 5 years were respectively 7.9 (6.3-9.8) gr and 16.5 (13.8-18.9) gr in GC group, 8.7 (5.9-10.0) gr and 16.5 (13.2-20.7) gr in MTX group, 7.1 (5.5-8.0) gr and 13.3 (12.8-13.7) gr in early-TCZ and 7.7 (6.2-11.1) gr and 19.7 (12.2-23.8) gr in late-TCZ.

Eighty-eight percent of patients developed at least one GC-AE, with infections and hypertension being the most common reported AEs (42% e 44%, respectively). Median GTI-CWS (Cumulative Worsening Score) after 1 year was 65 (20-137) in GC, 63 (10-95) in MTX, 51 (33-116) in TCZ-early, 44 (0-91) in TCZ-late. Median GTI-CWS after 5 years was 219 (118-240) in GC, 137 (65-206) in MTX, 147 (146-147) in TCZ-early, 200 (121-231) in TCZ-late. A correlation between GTI-CWS and the GC cumulative dose was found (after 5 years r: 0.295, p: 0.026).

Conclusion: Chronic GC treatment is associated with a high risk of developing comorbidities. GTI score demonstrated to be an effective tool to assess GC-related AEs and proved to correlate with GC cumulative dose.

TCZ confirmed its efficacy in reducing relapse rate, both in early and late-TCZ groups. TCZ showed for the first time in a real-life cohort a GC sparing effect, with a 19% reduction in GC cumulative dose and a 33% reduction in GTI-CWS in 5 years (comparing GC group *vs* early-TCZ group).

References: (1) Glucocorticoid Toxicity Index (Copyright © 2016, 2018. Massachusetts General Hospital. All rights reserved.) (2) Miloslavsky EM et al. Ann Rheum Dis. 2017 doi: 10.1136/annrheumdis-2016-210002.

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ACR Meeting Abstracts - https://acrabstracts.org/abstract/glucocorticoid-related-adverse-events-in-giant-cell-arteritis-application-of-the-glucocorticoid-toxicity-index-in-a-monocentric-cohort-of-140-patients/

1.8 STUDY ON TREG E TH17 AS BIOMARKERS IN GIANT CELL ARTERITIS AND POTENTIAL EFFECTS OF THE TREATMENT

1.8.1 AIM OF THE STUDY

The pathogenesis of GCA is not fully understood, but major progresses have been made in recent years focusing on the immune cell abnormalities. Research studies have shown that both the innate and adaptive immune systems are dysregulated in GCA patients. Considering the innate counterpart, macrophages play a central role, particularly for the granuloma and multinucleated giant cells formation, which are pathognomonic features of arterial lesions in GCA [116], as well as in IL-1 and IL-6 production. In a similar way, neutrophils and dendritic cells (DCs) play a crucial role in the pathogenesis of GCA. Neutrophils are locally activated as consequence of the arterial wall damage to release pro-inflammatory cytokines, including IL-6 [117] and IL-17A, and to produce enzymes and neutrophil extracellular traps (NETs) that disrupt the extracellular matrix, as observed in temporal artery biopsies of GCA patients [118]. DCs, located between the media and adventitia of the arterial wall, contribute to macrophages and T lymphocytes activation, triggering cytokines production and granuloma formation [119].

Evidence also supports the involvement of adaptive immunity in GCA pathogenesis, with dysregulation observed in both B and T lymphocytes. Regarding B cells, their role in GCA is currently not fully understood. Plasma cells have been observed in positive temporal artery biopsies [120], but the potential impact of humoral immunity in GCA remains undetermined. It is more likely to consider that their primary role is in T cell responses regulation through the secretion of both pro-inflammatory (TNF-α and IL-6) and anti-inflammatory (IL-10) cytokines [121].

Two CD4+ T effector cell subtypes have been identified essential in the pathogenies of this disease: type 17 helper T cells (Th17) and type 1 helper T cells (Th1), both of which are expanded in peripheral blood and arteries of GCA patients [122,123]. Th1 cells, differentiated via the IL12/IFN-γ axis, produce IFN-γ [124] and are involved in ischemic vascular injury but they are not sensitive to steroid therapy [123]. Th17 cells are responsible for IL-17 production, an interleukin that facilitates

macrophage recruitment and induces the production of many pro-inflammatory molecules, such as IL-1, IL-6, IL-17, IL-23 and chemokines [125]. Unlike Th1 cells, Th17 cells are sensitive to steroid therapy.

It is important to note that in GCA, not only Th1 and Th17 cells are in excess, but the imbalance between these two proinflammatory cell subsets and regulatory T cells (Tregs) is crucial for the pathogenesis of the disease. Tregs play a key role in maintaining immune tolerance and preventing autoimmunity. They are reduced in both the blood and arterial lesions of patients with GCA [126]. Furthermore, Tregs in GCA patients appear functionally impaired and potentially pathogenic, exhibiting reduced proliferation and elevated IL-17 production compared to healthy individuals [127]. Interestingly, while GC therapy is ineffective in inhibiting these pathogenic Tregs in GCA [126], therapeutic blockade of the IL-6 receptor (IL-6R) has been shown to revert the Treg abnormalities detected in active GCA and restore Treg anti-inflammatory function [127].

This study aimed to analyze the number of circulating Th17 and Treg cells in a cohort of GCA patients before and after tocilizumab treatment, correlating these findings with disease activity and therapeutic response.

1.8.2 METHODS

Eight consecutive patients with a diagnosis of GCA, based on the 2022 ACR/EULAR criteria [59] , were enrolled at the Department of Rheumatology and Clinical Immunology in Brescia, Italy. At the time of enrollment, patients had active disease, defined by specific signs/symptoms and abnormalities in laboratory or imaging studies (temporal artery ultrasound or PET). All patients were on steroid therapy and began treatment with tocilizumab 162 mg sc/week according to clinical practice guidelines. After 6 months of treatment, disease activity and response to treatment were assessed by an expert rheumatologist. Patients were defined as in remission and therefore classified as responders if they showed no signs or symptoms of active GCA, and, when appropriate, imaging showed no signs of disease activity. Patients were defined as non-responders if, after 6 months of therapy, they presented with signs or symptoms of active GCA and/or, when appropriate, imaging indicated signs of disease activity.

Clinical, laboratory, and demographic data were obtained from medical records at diagnosis, at the start of tocilizumab therapy (T0), and after 6 months of treatment with TCZ (T6). Additionally, a study of T-cells immunophenotype was conducted at both T0 and T6.

Immunophenotypic characterization was performed on Peripheral Blood Mononuclear Cells (PBMCs), extracted from peripheral blood using a standard protocol. Lymphocyte surface markers were evaluated by flow cytometry (FACS Canto II BD cytometer), using fluorochrome-conjugated monoclonal antibodies (Beckman Dickinson FITC-CD3, PE-CD25, PerCPCY5.5-CCR10, PE-Cy7-CXCR3, ALEXA 647-CD127, APC-H7-CD4, BV421-CCR4, BV480-CCR6) to identify lymphocyte subpopulations. FlowJo v.10 was used for the analysis. Cells were defined as follows:

- Th17: CD3+CD4+CCR4+CXCR3-CCR6+CCR10-
- Treg: CD3+CD4+CD25highCD127low

Data were presented as median (1st-3rd interquartile) or percentage composition for continuous and categorical variables, respectively. Fisher's exact test was employed to compare qualitative variables, while Mann-Whitney U test was used to compare continuous variables between groups. Variations from baseline to different timepoints were assessed using Wilcoxon's signed rank test for paired samples. Statistical analysis was performed with GraphPad statistical software package (GraphPad Software, Inc, CA, USA). A two-tailed P-value less than alpha reference of 0.05 was considered statistically significant.

1.8.3 RESULTS

1.8.3.1 DEMOGRAPHIC AND CLINICAL FEATURES

Eight patients were enrolled in the study: 5 patients were females (63%) and 3 were males (37%) with a median age at diagnosis of 75 (72-79) years (Table 14). GCA clinical phenotype was C-GCA (50%) in 4 patients, LV-GCA in 1 (13%), and C-LV-GCA in 3 (37%). Median time between diagnosis and TCZ start (T0) was 12 (7-21) weeks. In 4 patients TCZ was introduced within 3 months after diagnosis for persistent active disease and/or contraindications to prolonged high dose GCs; in 4

patients TCZ was introduced at least 3 months after diagnosis for GCA relapses (time between diagnosis and T0 22 (18-25) weeks).

After 6 months of treatment with TCZ (T6), 6 patients were classified as responder while 2 was considered non-responder for persistence of signs or symptoms of active GCA. Comparing the two groups of patients, no significant differences emerged in terms of age, sex, or clinical manifestations of the disease at onset.

At TCZ start (T0), all patients were on treatment with GCs, with a median dose of 31 (23-45) mg/day. This dosage was progressively reduced in all patients and after 6 months of treatment with TCZ (T6), the median dose was 10 (8-11) mg/day.

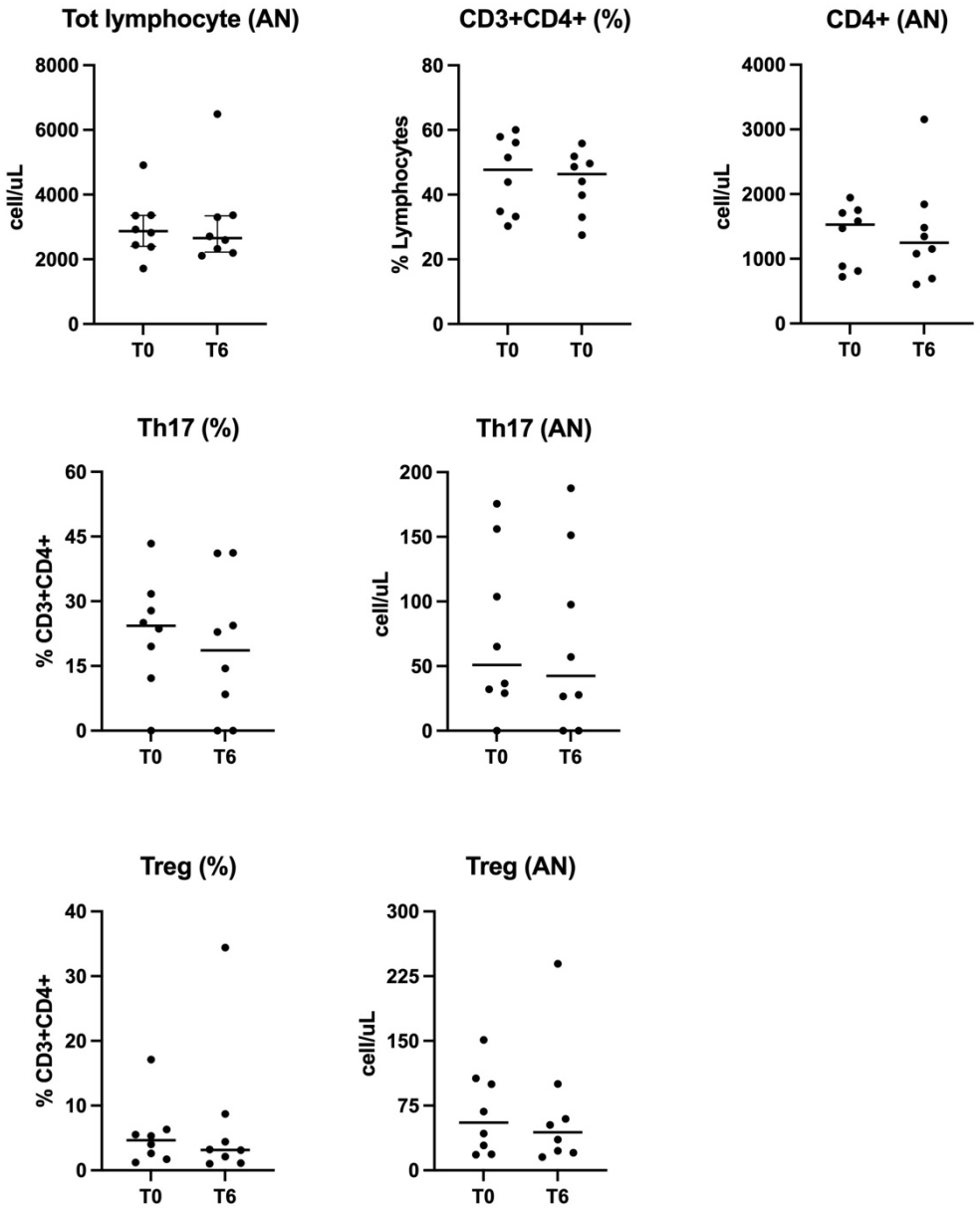
Clinical data	GCA (n: 8)	Responder (n: 6)	NO responder (n: 2)	p
Sex (F/M)	5 (63%) /3 (37%)	3 (50%) / 3 (50%)	2 (100%) /0 (0%)	0,4643
Age at diagnosis (years)	75 (72-79)	73 (72-75)	82 (79-85)	0,2405
C-GCA	4 (50%)	2 (33%)	2 (100%)	0,4286
LV-GCA	1 (13%)	1 (17%)	0 (0%)	0,5371
LC-C-GCA	3 (37%)	3 (50%)	0 (0%)	0,4643
Headache	6 (75%)	4 (67%)	2 (100%)	0,3458
Scalp tenderness	6 (75%)	4 (67%)	2 (100%)	0,3458
Jaw claudication	4 (50%)	2 (33%)	1 (50%)	0,6733
Ocular involvement	4 (50%)	3 (50%)	1 (50%)	0,9999
Fever	2 (25%)	2 (33%)	0 (0%)	0,3458
Weight loss	5 (63%)	4 (67%)	1 (50%)	0,6733
Fatigue	6 (75%)	5 (83%)	1 (50%)	0,3458
PMR	7 (87%)	6 (100%)	1 (50%)	0,0641
Time before TCZ (w)	12 (7-21)	12 (5-21)	14 (11-17)	0,8668
GCs dose at T0 (mg/day)	31 (23-45)	28 (20-41)	41 (36-45)	0,3990
CRP at T0 (mg/mL)	4 (0-5)	4 (0-4)	7 (4-11)	0,8407

Table 14. Demographic characteristics and disease manifestations at diagnosis. GCs: glucocorticoids, CRP: C-reactive protein. Data expressed as n (%) or median (IQR)

1.8.3.2 PHENOTYPIC ANALYSIS OF T-CELLS

T lymphocyte subpopulations analysis is shown in Graphic 6 and Tables 15 and 16.

The following parameters were evaluated: absolute number of total lymphocytes, absolute number and percentage of CD3+CD4+, Th17 and Tregs.



Graph 6. T lymphocyte subpopulations at TCZ start (T0) and after 6 months (T6) Data expressed as median.

A longitudinal comparison of paired data between T0 and T6 was performed (Table 14, Graph 6). After the initiation of TCZ therapy, a reduction was observed in both the absolute number and percentage of Th17 and Tregs, although without statistically significant differences. Specifically, Th17 cells decreased from 24.3% (17.7 - 28.8) to 18.7% (6.3 - 28.6) and from 50.8 (31.3 - 116.9) cells/uL to 42.4 (19.9 - 111) cells/uL (p: 0.2969 and p: 0.5781, respectively). Tregs, on the other

hand, decreased from 4.6% (2.3 - 5.7) to 3.1% (1.8 - 5.5) and from 55.3 (26.3 - 101.6) cells/uL to 44.1 (22 - 69.7) cells/uL (p: 0.7422 and p: 0.9453, respectively).

T Lymphocytes subpopulations	T0 (n: 8)	T6 (n: 8)	p
Lymphocytes tot (cell/uL)	2871,0 (2428,8 - 3353,0)	2654,0 (2288,5 - 3315,5)	0,7422
CD3+CD4+ (% Lymphocytes)	47,7 (34,4 - 56,6)	46,4 (38,1 - 50,2)	0,6406
CD3+CD4+ (cell/uL)	1526,9 (865,6 - 1719,5)	1247,5 (983,8 - 1572,3)	0,8438
Th17 (% CD3+CD4+)	24,3 (17,7 - 28,8)	18,7 (6,3 - 28,6)	0,2969
Th17 (cell/uL)	50,8 (31,3 - 116,9)	42,4 (19,9 - 111)	0,5781
Treg (% CD3+CD4+)	4,6 (2,3 - 5,7)	3,1 (1,8 - 5,5)	0,7422
Treg (cell/uL)	55,3 (26,3 - 101,6)	44,1 (22 - 69,7)	0,9453

Table 15. T lymphocyte subpopulations at TCZ start (T0) and after 6 months (T6). Data expressed as median (IQR)

In the second part of the study, a comparison was made between patients classified as responders and those classified as non-responders (Table 16). The comparison between the two groups did not show significant differences at T0 or T6. However, it was found that in the responder group, the percentage of Th17 cells decreased after the start of therapy and disease remission (from 26.4% [15.4 - 30.7] to 15.7% [2.1 - 36.6]), whereas this did not occur in non-responder patients (from 21.6% [20.5 - 22.6] to 19.4% [16.9 - 21.9]).

T Lymphocytes subpopulations	Responder T0 (n: 6)	No-responder T0 (n: 2)	p	Responder T6 (n: 6)	No-responder T6 (n: 2)	p
Lymphocytes tot (cell/uL)	2871,0 (2537,8 - 3242,5)	2874,0 (2630,0 - 3118,0)	0,9999	2810,0 (2225,5 - 3346,5)	2654,0 (2624,5 - 2683,5)	0,9999
CD3+CD4+ (% Lymphocytes)	47,7 (37,1 – 55,0)	44,1 (37,2 - 51)	0,8571	46,4 (35,8 - 49,4)	45,8 (42,8 - 48,8)	0,8571
CD3+CD4+ (cell/uL)	1526,9 (1030,5 - 1677,3)	1334,8 (1028,9 - 1640,7)	0,9999	1316,7 (809,7 - 1751,7)	1212 (1145,9 - 1278,1)	0,8571
Th17 (% CD3+CD4+)	26,4 (15,4 - 30,7)	21,6 (20,5 - 22,6)	0,6429	15,7 (2,1 - 36,6)	19,4 (16,9 - 21,9)	0,8668
Th17 (cell/uL)	50,8 (33,2 - 133,3)	66,4 (47,7 - 85,1)	0,8571	62,6 (6,9 - 137,9)	41,8 (34,2 - 49,4)	0,8668
Treg (% CD3+CD4+)	4,6 (2,2 – 6,0)	4,0 (3,3 - 4,8)	0,9999	3,1 (1,6 - 7,3)	3,3 (2,7 - 3,8)	0,9999
Treg (cell/uL)	55,3 (32,3 - 91,9)	62,6 (40,5 - 84,6)	0,9999	44,1 (24,2 - 88,2)	41,1 (31,8 - 50,3)	0,9999

Table 16. T lymphocyte subpopulations at TCZ start (T0) and after 6 months (T6) in responder and no-responder patients. Data expressed as median (IQR)

1.8.4 DISCUSSION

A dysregulation between proinflammatory CD4+ T cell subsets, such as Th17 cells, and regulatory T cells (Tregs) is believed to contribute to the development of GCA. Both Th17 cells and Tregs originate from the same naive CD4+ T cell precursor, with transforming growth factor-β (TGF-β) playing a key role in their differentiation. When proinflammatory signals, like IL-6 or IL-21, are present, TGF-β-stimulated CD4+ T cells are directed to differentiate into Th17 cells [127]. In contrast, in a non-inflammatory setting, these TGF-β-stimulated precursors differentiate into Tregs. Th17 cells, known for their proinflammatory role, are found within inflammatory infiltrates of the arteries and are elevated in the peripheral blood of patients with active, untreated GCA [123]. Tregs, which normally function to sustain immune tolerance and prevent autoimmunity, are reduced in both the blood and arterial tissue of individuals with GCA. Additionally, in comparison to healthy controls, Tregs in GCA patients show impaired function, marked by reduced proliferation and increased IL-17 production, suggesting they may be defective and potentially contribute to disease pathology [126,127]. Furthermore, under specific circumstances, fully differentiated Tregs may lose their suppressive function and become IL-17-producing cells (pathogenic pro-inflammatory Treg) [128,129].

There is a pressing need for reliable biomarkers in GCA, as they are currently lacking. Peripheral blood flow cytometry presents a practical option, being relatively easy to perform and accessible in clinical settings. Furthermore, identifying biomarkers that are not overly complex is beneficial, as markers like Tregs are already assessed in the context of other disease diagnostics, such as immunodeficiency, with adult reference ranges increasingly becoming available.

In light of the need for accessible biomarkers in GCA, we conducted a phenotypic analysis of T lymphocyte subpopulations, focusing specifically on Th17 and Treg cells, given their potential involvement in GCA pathogenesis.

The first finding that emerged from our study was lymphocytosis, observed at baseline and further increased at T6. This lymphocytosis may be attributable to the inflammatory nature of GCA, as inflammatory diseases are often associated with

elevated lymphocyte counts. Additionally, both steroid therapy and TCZ treatment could contribute to an increase in circulating lymphocytes.

Regarding the Th17 subpopulation, we observed a decrease between T0 and T6. This result aligns with expectations, as Th17 cells are proinflammatory, and a reduction was anticipated following therapy when patients transitioned from an active disease state (with ongoing inflammation) to an inactive state (without inflammation). This hypothesis is further supported by the observation that the reduction in Th17 cells was more pronounced in patients classified as responders, meaning those who achieved complete clinical remission of GCA symptoms and normalization of imaging findings. In these patients, who were in clinical remission, a parallel immunological remission, or at least a less inflammatory profile, was observed. In contrast, non-responders did not exhibit a similar reduction in Th17 cells, possibly highlighting a correlation between the persistence of active disease and proinflammatory alterations at the immunological level.

In our cohort, we did not observe significant changes in the Treg population, aside from a slight trend toward reduction. Interpretation of this finding is challenging, as this study assessed only the total number of Tregs without distinguishing specific subpopulations, some of which may exhibit a proinflammatory phenotype. This limitation highlights the need for a more comprehensive analysis that examines Treg subpopulations rather than considering total Tregs alone.

Additional limitations of our study include the small sample size and the lack of functional assays, which would have provided a deeper understanding of T cell functionality and immune response in GCA.

1.8.5 CONCLUSION

There is an urgent demand for reliable biomarkers in GCA, as these are currently absent. Peripheral blood flow cytometry offers a feasible solution, being relatively straightforward and readily available in clinical environments. With the aim of identifying new biomarkers in GCA, we performed a phenotypic analysis of T lymphocyte subpopulations, with a particular focus on Th17 and Treg cells due to their potential role in the disease's pathogenesis. One of the key findings from our study was the presence of lymphocytosis, noted at baseline and further increasing

by T6. This lymphocytosis may reflect the inflammatory characteristics of GCA, with both steroid therapy and TCZ treatment potentially contributing to the rise in circulating lymphocytes. Concerning the Th17 subpopulation, we documented a decline between T0 and T6, which is consistent with expectations since Th17 cells are proinflammatory. This reduction aligns with the shift from an active disease state, characterized by ongoing inflammation, at baseline to an inactive state post-therapy at T6. Notably, the decrease in Th17 cells was more pronounced in patients identified as responders.

While we did not observe significant changes in the Treg population, there was a slight trend toward reduction, although specific subpopulations were not distinguished.

This study highlights that lymphocyte subpopulations could serve as indicators of disease activity and as potential predictors of drug response. However, these findings are still preliminary and will necessitate further investigation in the future.

SECTION 2:

COMPLEMENTARY RESEARCH ACTIVITIES ON SYSTEMIC VASCULITIDES

2.1 BACKGROUND

Systemic vasculitides represent a group of disorders characterized by inflammation of blood vessels, affecting various organs and tissues. These diseases are classified based on the size and type of blood vessels affected and the underlying immunologic mechanisms. The primary classification approach divides vasculitides into three main categories: large-vessel vasculitides, medium-vessel vasculitides, and small-vessel vasculitides. Large-vessel vasculitides include GCA and Takayasu Arteritis (TA), which primarily involve the aorta and its major branches. Medium-vessel vasculitides, such as Polyarteritis Nodosa (PAN) and Kawasaki Disease, predominantly affect medium-sized arteries, leading to organ ischemia and inflammation. Small-vessel vasculitides primarily involve small arteries, arterioles, capillaries, and venules and are often associated with specific autoantibodies, like antineutrophil cytoplasmic antibodies (ANCA).

ANCA-associated vasculitides (AAV) form a subgroup within small-vessel vasculitides and include Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), and Eosinophilic Granulomatosis with Polyangiitis (EGPA). These diseases are characterized by the presence of ANCAs, in almost 80% of patients. The two primary types of ANCAs detected are myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. GPA is most often associated with PR3-ANCA, while MPA is typically associated with MPO-ANCA. EGPA is less strongly associated with ANCAs, as only about 40% of patients present with MPO-ANCA, making its pathogenesis unique among the AAVs. Each of these diseases demonstrates distinct clinical manifestations, but they share a tendency to cause rapidly progressive damage, particularly to the kidneys and lungs.

Specifically, EGPA, also known as Churg-Strauss Syndrome, is a rare, multisystem disorder characterized by asthma, eosinophilia, and necrotizing vasculitis affecting small to medium-sized vessels. EGPA is often classified within AAV due to its overlap in clinical and immunologic features with other ANCA-associated vasculitides. However, EGPA differs in its hallmark eosinophilic infiltration and asthma, which are not typically seen in GPA or MPA. EGPA frequently presents in three phases: a prodromal phase marked by allergic rhinitis and asthma, an

eosinophilic phase with tissue infiltration by eosinophils, and a vasculitic phase characterized by systemic small-vessel inflammation. This eosinophil-driven inflammation links EGPA with hypereosinophilic syndromes (HES), a group of disorders characterized by prolonged eosinophilia and organ damage due to eosinophil infiltration.

HES encompass a spectrum of eosinophil-related conditions, including both idiopathic HES and primary eosinophilic disorders associated with genetic mutations or hematological proliferative diseases. These disorders often affect multiple organs, particularly the heart, lungs, and gastrointestinal tract. While both EGPA and HES involve eosinophilia, EGPA is distinguished by its vasculitic component and association with asthma and often MPO-ANCAs. The overlap between EGPA and other hypereosinophilic syndromes continues to be an area of active research, as understanding these distinctions may lead to improved diagnostics and targeted therapeutic approaches. Recognizing the unique features of each AAV subtype, particularly EGPA and its relation to hypereosinophilic conditions, is essential for developing tailored treatment strategies and improving patient outcomes. Given that EGPA and HES share the common feature of hypereosinophilia, they also partially overlap in their therapeutic approaches. Treatments for both conditions typically aim to reduce eosinophil levels to prevent organ damage and improve clinical outcomes. Among the key therapies is mepolizumab, a monoclonal antibody targeting interleukin-5 (IL-5), a cytokine crucial for eosinophil growth, differentiation, and survival. By blocking IL-5, mepolizumab effectively reduces eosinophil counts and is approved for use in both EGPA and specific forms of HES. In EGPA, mepolizumab has been shown to aid in achieving disease remission and reducing the need for systemic corticosteroids, which are traditionally used but associated with significant long-term side effects. For HES, mepolizumab likewise helps manage eosinophil-driven symptoms, particularly in patients with severe or refractory disease. This shared therapeutic strategy underscores the overlapping pathophysiology of EGPA and HES and highlights the potential of biologic agents like mepolizumab to improve treatment outcomes across eosinophilic disorders.

Section 2 of the thesis includes studies and research projects focused on systemic vasculitides distinct from GCA. In particular, it presents single-center and multicenter collaborative studies on EGPA with eosinophilic- related disorders, and ANCA-associated vasculitides (AAV).

2.2 STUDIES ON EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS AND EOSINOPHILIC-RELATED DISEASES

In the following chapters, single-center and multicenter collaborative studies on EGPA and eosinophilic-related disorders will be presented. The studies included are as follows:

- Glucocorticoid-sparing effect of Mepolizumab: real life experience in a monocentric cohort of patients affected by Eosinophilic Granulomatosis with Polyangiitis

- Mepolizumab efficacy in Eosinophilic gastroenteritis

- Impact of Mepolizumab on patient-reported outcomes in Eosinophilic Granulomatosis with Polyangiitis by using the ANCA-associated vasculitis patient-reported outcomes (AAV-pro) questionnaire: a European multicentre prospective study

- Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis: a European multicenter observational study.

- Clinical picture, outcomes, and predictors of relapse in eosinophilia-associated coronary vasospasm: Data from a European multicentric study.

- Ophthalmic vascular manifestations in eosinophil-associated diseases: a comprehensive analysis of 57 patients from the CEREO and EESG networks and a literature review.

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Glucocorticoid-sparing effect of Mepolizumab: real life experience in a monocentric cohort of patients affected by Eosinophilic Granulomatosis with Polyangiitis

Francesca Regola, Stefania Bertocchi, Marco Taglietti, Franco Franceschini, Paola Toniati.

Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia, Italy.

Background/ Objectives: Oral glucocorticoids (GC) are the mainstay of treatment for eosinophilic granulomatosis with polyangiitis (EGPA) but chronic exposure to GC is associated with serious comorbidities. Mepolizumab (MEPO) demonstrated to be an efficacious treatment for EGPA in the randomized controlled MIRRA trial [1]. ACR guidelines suggest treating non-severe EGPA with MEPO associated with GC as first choice and adding MEPO in non-severe relapses occurred while receiving other immunosuppressants. There are insufficient data to support dosages and duration of GC treatment during MEPO treatment, although guidelines suggest prescribing the minimum effective dose to minimize GC toxicity [2].

The aim of the study was to evaluate the GC-sparing effect of MEPO in a monocentric cohort of patients affected by EGPA.

Methods: We enrolled 26 patients affected by EGPA according to MIRRA criteria and/or ACR criteria [1][3]. We compared cumulative GC dosage prescribed in the 6 months before beginning treatment with MEPO to the cumulative dosage prescribed in the 6 months after starting MEPO. We also analyse MEPO efficacy comparing median number of asthma attacks, BVAS and VDI.

Results: Twenty-six patients (M/F 16/10) affected by EGPA were diagnosed at a median age of 57 years (IQR 47-65) and started therapy with MEPO after a median disease duration of 6 (1.5-10) years. Overall clinical features of patients at diagnosis (Td), at MEPO starting (T0) and after 6 months of MEPO (T6) are described in table 1a. At MEPO starting (T0), 24/26 (92.3%) were treated with GC and 13/26 (50%) were on treatment with other immunosuppressants (1 cyclosporine, 2 methotrexate, 3 mycophenolate, 7 azathioprine). The cumulative GC dosage administered to patients in the six months after MEPO starting was significant lower if compared with dosage in the prior six months. After MEPO starting, there was also a significant reduction of asthmatic symptoms and BVAS score, with no increasing in VDI score (table 1b and 1c).

Conclusions: In our cohort MEPO had a significant GC-sparing effect and significantly reduced asthma manifestations and disease activity.

References:

1. Wechsler et al, N Engl J Med. 2017 May 18;376(20):1921-1932.
2. Chung et al, Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.
3. Masi et al, Arthritis Rheum. 1990 Aug;33(8):1094-100.

Disclosures: None.

1a. Clinical features

	Td	T0	T6
Constitutionalsymptoms	12 (46%)	1 (4%)	1 (4%)
Cutaneous	9 (35%)	1 (4%)	0 (0%)
Ear, nose, throat	22 (85%)	9 (35%)	5 (19%)
Pulmonary	25 (96%)	18 (69%)	1 (4%)
Cardiovascular	6 (23%)	1 (4%)	0 (0%)
Gastrointestinal	4 (15%)	1 (4%)	0 (0%)
Neurological	14 (54%)	6 (23%)	2 (8%)
Renal	0 (0%)	0 (0%)	0 (0%)

1b. Disease activity before MEPO starting (T0) and after 6 months (T6)

	T0	T6	p
BVAS	2 (0-2)	0 (0-0)	0.0005*
VDI	2 (1.3-3)	2 (1.3-3)	0.5716

1c. Comparison of asthma activity and GC therapy between the 6 months before and the 6 months after MEPO starting (T0)

	In the 6 months before T0	In the 6 months after T0	p
GC cumulative dose (mg)	1376 (821-2045)	964 (521-1561)	0.0005*
GC daily dose (mg/day)	8 (5-11)	5 (3-9)	0.0007*
Patients with active asthma	18 (69%)	1 (4%)	0.0211*

Data express as median (IQR) or n (%). * p value < 0.05
BVAS: Birmingham vasculitis activity index, VDI: Vasculitis damage index.

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Mepolizumab efficacy in Eosinophilic gastroenteritis

Francesca Regola, Stefania Bertocchi, Franco Franceschini, Paola Toniati.

Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia, Italy.

Background/ Objectives: Eosinophilic gastroenteritis (EGE) is defined as an immune-mediated inflammatory disorder characterized by an eosinophilic infiltrate in one or more organs of the gastrointestinal (GI) tract, as stomach, small intestine, and colon. EGE is usually idiopathic, but it can be also a manifestation of a systemic eosinophilic disease, such as Eosinophilic granulomatosis with polyangiitis (EGPA) and Hypereosinophilic syndrome (HES).

Mepolizumab (MEPO), a monoclonal antibody targeting interleukin-5 (IL-5), a key haematopoietin needed for eosinophil development and function, has been recently approved both for EGPA and HES [1]. To date there are no specific data on MEPO efficacy in EGE manifestation in patients with these diseases.

The aim of the study was to analyse MEPO efficacy in a cohort of HES and EGPA patients with GI involvement.

Methods: Five patients with EGE associated with EGPA (define according 2022 ACR/EULAR criteria [1]) or HES and treated with MEPO for active GI disease were enrolled in the study. Data were collected from clinical charts at diagnosis, at MEPO starting and after 12 months of treatment. MEPO efficacy, safety and steroid-sparing effect were analysed.

Results: Two patients had a diagnosis of EGPA, and three had a diagnosis of HES (table 1). Both patients with EGPA presented at diagnosis asthma, nasal polyps and eosinophilia; one had also pericarditis and purpura; the other one had multiple neuritis. In the group of patients with HES, two patients presented also pulmonary infiltrates. All three HES patients at diagnosis presented severe eosinophilia but myeloproliferative clonal variants of HES were excluded. All 5 patients presented GI involvement, confirmed by biopsy and histological examination. The most frequently involved organs were stomach, duodenum and colon and the most reported symptoms were abdominal pain, weight loss, nausea, bloody and/or mucous diarrhea.

All 5 patients presented active GI disease and were on treatment with systemic glucocorticoids when started treatment with MEPO 300 mg monthly. After MEPO starting all patients showed a clinical improvement, with reduction of symptoms until complete resolution. At the same time, in all patients glucocorticoids dose was reduced from a median dose of 12,5 (5-37,5) mg/day to 3 (0-3) mg/day (p: 0.015). No significant side effects were reported in the follow-up.

Conclusions: In this cohort MEPO demonstrated its efficacy in treating GI manifestations in patients with EGPA and HES, showing also a significant GC-sparing effect and a good safety profile.

References:

1. Wechsler et al, N Engl J Med. 2017 May 18;376(20):1921-1932.
2. Grayson PC, et al. Ann Rheum Dis. 2022 Mar;81(3):309-314.

Disclosures: None.

Nr patient	Sex / Age at diagnosis	Diagnosis	EOS at diagnosis (cell/mmc)	GI involvement	Other organ involvements at diagnosis	Time between diagnosis and MEPO starting	Active disease manifestation at MEPO starting
1	M / 68	EGPA	1120	Colon	Asthma, nasal polyps, pericarditis, purpura	3	Asthma, nasal polyps, colon
2	M / 36	EGPA	4560	Stomach, duodenum, colon	Asthma, nasal polyps, multiple neuritis	10	Asthma, nasal polyps, colon
3	F / 64	HES	3200	Stomach, colon	Pulmonary infiltrates	2	Stomach, colon
4	F / 62	HES	8150	Stomach, duodenum	nd	1	Stomach, duodenum
5	M / 68	HES	8500	Stomach, duodenum	Pulmonary infiltrates	1	Stomach, duodenum

ABSTRACT NUMBER: 1611

Impact of Mepolizumab on Patient-reported Outcomes in Eosinophilic Granulomatosis with Polyangiitis by Using the ANCA-associated Vasculitis Patient-reported Outcomes (AAV-PRO) Questionnaire: A European Multicentre Prospective Study

Paolo Delvino[1], Luca Quartuccio[2], Joanna Robson[3], Federico Alberici[4], Diego Bagnasco[5], Alvise Berti[6], Marco Caminati[7], Marta Camoni[8], Maria Cid[9], Edoardo Conticini[10], Giulia Costanzo[11], Claire de Moreuil[12], Stefano Del Giacco[11], Georgina Espigol-Frigole[13], Virginia V Ferretti[14], Franco Franceschini[15], Luca Iorio[16], Anna Kernder[17], Catherine Klersy[14], Alberto Lo Gullo[18], Laura Losappio[19], Elena Manna[20], Matteo Maule[21], Carlomaurizio Montecucco[22], Negrini Simone[23], Roberto Padoan[24], Francesca Regola[25], Luisa Ricciardi[26], Jan Schroeder[19], Benjamin Terrier[27], Paola Toniati[28], Elena Treppo[2], Maria-Letizia Urban[29], Augusto Vaglio[30], Giacomo Emmi[31] and Sara Monti[32], and European EGPA Study Group, [1]University of Milano-Bicocca, Milan, Milan, Italy, [2]Division of Rheumatology, Department of Medicine (DMED), University of Udine, Udine, Italy, Udine, Italy, [3]UWE Bristol, Bristol, United Kingdom, [4]Nephrology Unit, University of Brescia, ASST Spedali Civili, University of Brescia, Brescia, Italy, Brescia, Italy, [5]Allergy and Respiratory Diseases, Department of Internal Medicine (DIMI), IRCCS Policlinico San Martino, Genoa, Italy, [6]University of Trento, Rochester, Italy, [7]Department of Medicine, Asthma, Allergy and Clinical Immunology Section, University of Verona, Verona, Italy, [8]Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy, [9]Hospital Clinic Barcelona. University of Barcelona, Barcelona, Spain, [10]University of Siena, Siena, Siena, Italy, [11]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy, [12]Service de médecine interne, CHU de Brest, Brest, France, [13]Hospital Clinic de Barcelona, Barcelona, Spain, [14]Biostatistcs & Clinical Trial Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Pavia, Italy, [15]Scleroderma Unit, Rheumatology and Clinical Immunology Unit, ERN ReCONNET, ASST Spedali Civili, Brescia, Italy, Brescia, Italy, [16]Rheumatology Unit, Department of Medicine DIMED, University of Padua, Padova, Italy, Padova, Italy, [17]HHU Dusseldorf, Dusseldorf, Germany, [18]Rheumatology Unit, Papardo Hospital, Messina, Italy, [19]Division of Allergy and Clinical Immunology, ASST GOM Niguarda, Milan, Milan, Italy, [20]Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Pavia, Italy, [21]Asthma Center and Allergy Unit, Verona Integrated University Hospital, Verona, Verona, Italy, [22]IRCCS policlinico S. Matteo foundation, University of Pavia, Pavia, Italy, [23]Department of Internal Medicine (DIMI), University of Genoa, Genoa, Genoa, Italy, [24]Department of Medicine DIMED, Division of Rheumatology, University of Padua, Padua, Italy, [25]Unit of Rheumatology and Clinical Immunology, ASST Spedali Civili Brescia and University of Brescia, Brescia, Italy, [26]Allergy and Immunology Unit, Department of Clinical and Experimental Medicine, G. Martino Teaching Hospital, University of Messina, Messina, Messina, Italy, [27]Service de Médecine interne, Hôpital Cochin, AP-HP, Paris, Ile-de-France, France, [28]Spedali civili, 25123, Italy, [29]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [30]Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Firenze, Florence, Italy, [31]University of Trieste, Trieste, Italy, [32]IRCCS Istituto Auxologico Italiano, Milan, Italy

Meeting: ACR Convergence 2024

Keywords: ANCA associated vasculitis, Eosinophilic Granulomatosus with Polyangiitis (Churg-Strauss), Patient reported outcomes

SESSION INFORMATION

Date: Sunday, November 17, 2024

Session Type: Poster Session B

Title: Vasculitis – ANCA-Associated Poster II

Session Time: 10:30AM-12:30PM

Background/Purpose: Mepolizumab (MEPO) proved its efficacy in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) in the randomized controlled MIRRA trial. The ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire is a novel, disease-specific tool, validated with the aim of assessing the impact of the disease and its treatment on the patients' perspectives. The aim of our study is to prospectively evaluate the impact and the rapidity of the effect of MEPO on the AAV-PRO score and patient global assessment (PtGA) in a multicentre cohort of patients with EGPA.

Methods: Patients with EGPA satisfying the 2022 ACR/EULAR and/or MIRRA trial classification criteria and initiating treatment with MEPO were included. PtGA and AAV-PRO score were prospectively evaluated at MEPO initiation and after 7, 14, 30, 90 and 180 days of treatment. Predictors of improved AAV-PRO response during treatment with MEPO were also investigated.

Results: Seventy patients were included in the study: female 54.3%, mean age at diagnosis 48.7±12.6 years, 20% ANCA-positive. Sixty-three patients (90%) had a history of relapsing disease. Forty-seven (67.1%) and 23 (32.9%) patients received MEPO 100 mg and 300 mg/4 weeks, respectively, with the main indication being refractory asthma and/or rhinosinusitis. Prednisone (PDN)-equivalent mean dose was 10.8±9.2 mg/day. At MEPO initiation, mean PtGA, AAV-PRO organ-specific symptoms, systemic symptoms, treatment side effects, social and emotional impact, concerns about the future and physical function domain 0-100 score were 59.1±21.2, 30.9±17.8, 25.5±18.6, 18.8±18.1, 32.6±21.9, 37.7±22.1 and 28.2±21.2, respectively. After 7 days, a statistically significant reduction of PtGA [ratio 0.87 (95% CI 0.87—0.95); Table 1] was observed. At 14 days, all AAV-PRO domains, except treatment side effects, showed a statistically significant improvement compared to baseline. Conversely, no relevant amelioration of the AAV-PRO domains was demonstrated between 30 and 180 days of follow-up (Figure 1). Previous history of vasculitic relapse, BVAS ≥3, C-reactive protein ≥5 mg/L and PDN-equivalent dose ≥10 mg/day at MEPO initiation were the main predictors of a better response of the AAV-PRO questionnaire during follow-up. MEPO 100 mg/4 weeks and female sex positively influenced organ-specific symptoms compared to MEPO 300 mg/4 weeks, although with a less significant improvement of the treatment side effects domain. Conversely, age, educational level and ANCA status at baseline had no impact on the AAV-PRO domains.

Conclusion: MEPO allows a quick and remarkable improvement of several aspects of health-related quality of life in patients with refractory EGPA.

	FOLLOW-UP (DAYS)	7 VS 0	14 VS 0	30 VS 0	90 VS 0	180 VS 0
OSS	Ratio	0.87	0.79	0.64	0.55	0.53
	Bonferroni (95% CI)	0.74—1.03	0.67—0.94	0.54—0.75	0.47—0.65	0.45—0.63
SS	Ratio	0.88	0.84	0.73	0.73	0.76
	Bonferroni (95% CI)	0.76—1.02	0.72—0.98	0.63—0.85	0.63—0.85	0.66—0.89
TSE	Ratio	0.93	0.89	0.77	0.71	0.66
	Bonferroni (95% CI)	0.75—1.15	0.71—1.10	0.62—0.95	0.57—0.88	0.53—0.82
SEI	Ratio	0.91	0.83	0.74	0.71	0.70
	Bonferroni (95% CI)	0.82—1.01	0.75—0.92	0.66—0.82	0.63—0.78	0.63—0.78
CAF	Ratio	0.95	0.90	0.83	0.77	0.76
	Bonferroni (95% CI)	0.88—1.03	0.83—0.97	0.77—0.90	0.71—0.84	0.70—0.82
PF	Ratio	0.88	0.79	0.67	0.62	0.57
	Bonferroni (95% CI)	0.73—1.05	0.66—0.95	0.56—0.80	0.52—0.75	0.47—0.68
PTGA	Ratio	0.87	0.83	0.70	0.61	0.58
	Bonferroni (95% CI)	0.79—0.95	0.76—0.91	0.64—0.77	0.56—0.67	0.53—0.63

Table 1. Comparison, at different timepoints, of the AAV-PRO domains 0_100 score, after log-normalization and adjustment for sex and age.

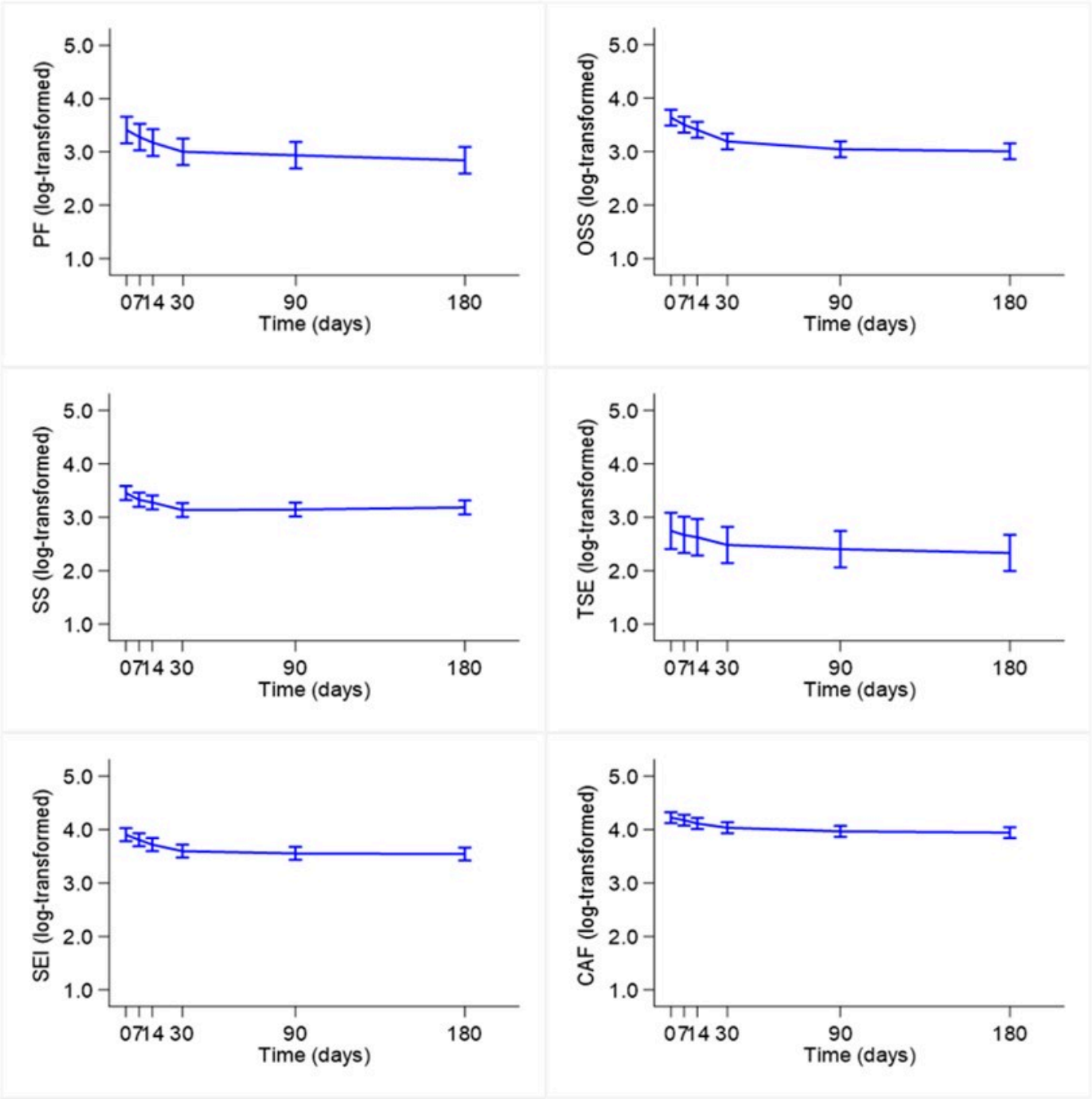

Figure 1. Temporal trend of the AAV-PRO specific domains 0_100 score during 6-month treatment with mepolizumab.

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American College of Rheumatology
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Mepolizumab for Eosinophilic Granulomatosis With Polyangiitis: A European Multicenter Observational Study

Alessandra Bettiol,[1] Maria Letizia Urban,[1] Lorenzo Dagna,[2] Vincent Cottin,[3] Franco Franceschini,[4] Stefano Del Giacco,[5] Franco Schiavon,[6] Thomas Neumann,[7] Giuseppe Lopalco,[8] Pavel Novikov,[9] Chiara Baldini,[10] Carlo Lombardi,[11] Alvise Berti,[12] Federico Alberici,[13] Marco Folci,[14] Simone Negrini,[15] Renato Alberto Sinico,[16] Luca Quartuccio,[17] Claudio Lunardi,[18] Paola Parronchi,[1] Frank Moosig,[19] Georgina Espígol-Frigolé,[20] Jan Schroeder,[21] Anna Luise Kernder,[22] Sara Monti,[23] Ettore Silvagni,[24] Claudia Crimi,[25] Francesco Cinetto,[26] Paolo Fraticelli,[27] Dario Roccatello,[28] Angelo Vacca,[29] Aladdin J. Mohammad,[30] Bernhard Hellmich,[31] Maxime Samson,[32] Elena Bargagli,[33] Jan Willem Cohen Tervaert,[34] Camillo Ribi,[35] Davide Fiori,[1] Federica Bello,[1] Filippo Fagni,[1] Luca Moroni,[2] Giuseppe Alvise Ramirez,[2] Mouhamad Nasser,[3] Chiara Marvisi,[36] Paola Toniati,[37] Davide Firinu,[5] Roberto Padoan,[6] Allyson Egan,[38] Benjamin Seeliger,[39] Florenzo Iannone,[8] Carlo Salvarani,[36] David Jayne,[38] Domenico Prisco,[1] Augusto Vaglio,[40] and Giacomo Emmi,[1] on behalf of the European EGPA Study Group

Objective. Mepolizumab proved to be an efficacious treatment for eosinophilic granulomatosis with polyangiitis (EGPA) at a dose of 300 mg every 4 weeks in the randomized, controlled MIRRA trial. In a few recently reported studies, successful real-life experiences with the approved dose for treating severe eosinophilic asthma (100 mg every 4 weeks) were observed. We undertook this study to assess the effectiveness and safety of mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks in a large European EGPA cohort.

Methods. We included all patients with EGPA treated with mepolizumab at the recruiting centers in 2015–2020. Treatment response was evaluated from 3 months to 24 months after initiation of mepolizumab. Complete response to treatment was defined as no disease activity (Birmingham Vasculitis Activity Score [BVAS] = 0) and a prednisolone or prednisone dose (or equivalent) of ≤4 mg/day. Respiratory outcomes included asthma and ear, nose, and throat (ENT) exacerbations.

Results. Two hundred three patients, of whom 191 received a stable dose of mepolizumab (158 received 100 mg every 4 weeks and 33 received 300 mg every 4 weeks) were included. Twenty-five patients (12.3%) had a complete response to treatment at 3 months. Complete response rates increased to 30.4% and 35.7% at 12 months and 24 months, respectively, and rates were comparable between mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks. Mepolizumab led to a significant reduction in BVAS score, prednisone dose, and eosinophil counts from 3 months to 24 months, with no significant differences observed between 100 mg every 4 weeks and 300 mg every 4 weeks. Eighty-two patients (40.4%) experienced asthma exacerbations (57 of 158 [36%] who received 100 mg every 4 weeks; 17 of 33 [52%] who received 300 mg every 4 weeks), and 31 patients (15.3%) experienced ENT exacerbations. Forty-four patients (21.7%) experienced adverse events (AEs), most of which were nonserious AEs (38 of 44).

Conclusion. Mepolizumab at both 100 mg every 4 weeks and 300 mg every 4 weeks is effective for the treatment of EGPA. The 2 doses should be compared in the setting of a controlled trial.

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[1]Alessandra Bettiol, PhD, Maria Letizia Urban, MD, Paola Parronchi, PhD, Davide Fiori, MD, Federica Bello, MD, Filippo Fagni, MD, Domenico Prisco, MD, Giacomo Emmi, MD, PhD: University of Florence, Florence, Italy; [2]Lorenzo Dagna, MD, Luca Moroni, MD, Giuseppe Alvise Ramirez, MD: San Raffaele Hospital, IRCCS, Vita-Salute San Raffaele University, Milan, Italy; [3]Vincent Cottin, PhD, Mouhamad Nasser, MD: Hospices Civils de Lyon and University of Lyon, Lyon, France; [4]Franco Franceschini, MD: ASST Spedali Civili of Brescia and University of Brescia, Brescia, Italy; [5]Stefano Del Giacco, MD, Davide Firinu, MD: University of Cagliari, Cagliari, Italy; [6]Franco Schiavon, MD, Roberto Padoan, MD: Azienda Ospedaliera-Universitaria di Padova, Padova, Italy; [7]Thomas Neumann, MD: Cantonal Hospital St. Gallen, St. Gallen, Switzerland, and Jena University Hospital, Jena, Germany; [8]Giuseppe Lopalco, MD, Florenzo Iannone, MD: Polyclinic Hospital, University of Bari, Bari, Italy; [9]Pavel Novikov, MD: Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is an antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis characterized by asthma, ear, nose, and throat (ENT) involvement, blood and tissue eosinophilia, and systemic vasculitis manifestations (1,2). Treatment mainly relies on systemic glucocorticoids and inhaled therapies for respiratory symptoms (3). EGPA usually follows a chronic relapsing course; thus, patients are at risk of permanent tissue or organ damage, which can also be due to glucocorticoid-related toxicity. Therefore, immunosuppressive treatments are often required and are also used as glucocorticoid-sparing agents (3,4).

Among novel therapeutic options, mepolizumab is a monoclonal antibody targeting interleukin-5 (IL-5), a cytokine involved in eosinophil maturation, differentiation, and survival. Increased serum levels of IL-5 are observed in eosinophilic disorders, including EGPA (5), and a genome-wide association study identified the *IL5* region as one of the main EGPA-associated loci (6).

Mepolizumab is approved for the treatment of severe eosinophilic asthma at 100 mg every 4 weeks subcutaneously (7) and for the treatment of hypereosinophilic syndrome (HES) at 300 mg every 4 weeks (8). After encouraging results from previous studies (9,10), the phase III MIRRA trial proved the efficacy of mepolizumab 300 mg every 4 weeks subcutaneously for relapsing or refractory EGPA (11,12), leading to its approval by the US Food and Drug Administration (FDA), while in Europe it is currently used off-label.

Recent smaller studies showed the successful use of mepolizumab 100 mg every 4 weeks for the treatment of EGPA, especially for the control of respiratory manifestations (13–15). However, the benefits and side effects of mepolizumab 100 mg every 4 weeks versus 300 mg every 4 weeks for systemic and respiratory EGPA involvement have never been compared. Therefore, its optimal dose is still debated (16). This study aimed to investigate the effectiveness and safety of mepolizumab 100 mg versus 300 mg every 4 weeks in a large European cohort of patients with EGPA.

PATIENTS AND METHODS

Study design and setting. This multicenter, retrospective study was conducted on a cohort of patients with EGPA treated with mepolizumab between May 2015 and February 2020 at 38 EGPA referral centers in 8 European countries (Italy, France, Germany, the UK, Russia, Spain, Switzerland, and Sweden; see Appendix A for members of the European EGPA Study Group). The study received approval from the University of Florence Ethics Committee (reference no. 16821_OSS).

Study population and treatment. The cohort included adult patients who met the American College of Rheumatology classification criteria for EGPA (17) or the criteria proposed in the MIRRA trial (11), who received mepolizumab 100 mg every 4 weeks or 300 mg every 4 weeks, in accordance with local practice. Patients with a follow-up of <3 months after the first mepolizumab dose or those enrolled in clinical trials were excluded.

Data collection and outcome assessment. Demographic, clinical, laboratory, and treatment-related data were retrospectively collected from medical records at the time of mepolizumab initiation (time 0) and at 3 months, 6 months, 12 months, and 24 months of follow-up. The effectiveness of mepolizumab in controlling systemic disease activity was assessed using the Birmingham Vasculitis Activity Score (BVAS) (18). Complete response to treatment was defined as no disease activity (BVAS = 0) and a prednisolone or

University, Moscow, Russia; [10]Chiara Baldini, MD: University of Pisa, Pisa, Italy; [11]Carlo Lombardi, MD: Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy; [12]Alvise Berti, MD: Santa Chiara Hospital and University of Trento, Trento, Italy; [13]Federico Alberici, PhD: University of Brescia and Spedali Civili Hospital, ASST Spedali Civili di Brescia, Brescia, Italy; [14]Marco Folci, MD: Humanitas Clinical and Research Center, IRCCS and Humanitas University, IRCCS, Milan, Italy; [15]Simone Negrini, MD: IRCCS Ospedale Policlinico San Martino and University of Genoa, Genoa, Italy; [16]Renato Alberto Sinico, MD: University of Milano Bicocca, Monza, Italy; [17]Luca Quartuccio, MD: University of Udine, Azienda sanitaria universitaria Friuli Centrale Udine, Udine, Italy; [18]Claudio Lunardi, MD: University of Verona, Italy; [19]Frank Moosig, MD: Rheumazentrum Schleswig-Holstein Mitte, Neumünster, Germany; [20]Georgina Espígol-Frigolé, MD: Hospital Clínic, University of Barcelona and Institut d'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain; [21]Jan Schroeder, MD: ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [22]Anna Luise Kernder, MD: Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [23]Sara Monti, PhD: Policlinico S. Matteo Fondazione, IRCCS, University of Pavia, Pavia, Italy; [24]Ettore Silvagni, MD: University of Ferrara, Ferrara, Italy; [25]Claudia Crimi, PhD: Policlinico-Vittorio Emanuele San Marco University Hospital, Catania, Italy; [26]Francesco Cinetto, MD: University of Padova, Padova, Italy; [27]Paolo Fraticelli, MD: University Hospital Ospedali Riuniti, Ancona, Italy; [28]Dario Roccatello, MD: San Giovanni Bosco Hospital and University of Turin, Turin, Italy; [29]Angelo Vacca, MD: Aldo Moro University of Bari, Bari, Italy; [30]Aladdin J. Mohammad, MD: Lund University, Skåne University Hospital, Lund, Sweden, and University of Cambridge, Cambridge, UK; [31]Bernhard Hellmich, MD: Medius Kliniken, University of Tübingen, Kirchheim unter Teck, Germany; [32]Maxime Samson, PhD: Dijon University Hospital, Dijon, France; [33]Elena Bargagli, MD: University of Siena, Siena, Italy; [34]Jan Willem Cohen Tervaert, PhD: University of Alberta, Edmonton, Alberta, Canada, and Maastricht University, Maastricht, The Netherlands; [35]Camillo Ribi, MD: University Hospital Center of Lausanne, Lausanne, Switzerland; [36]Chiara Marvisi, MD, Carlo Salvarani, MD: Azienda USL-IRCCS di Reggio Emilia, IRCCS, and Università di Modena e Reggio Emilia, Reggio Emilia, Italy; [37]Paola Toniati, MD: ASST Spedali Civili of Brescia, Brescia, Italy; [38]Allyson Egan, MD, David Jayne, MD: University of Cambridge, Cambridge, UK; [39]Benjamin Seeliger, MD: Hannover Medical School, Hannover, Germany; [40]Augusto Vaglio, PhD: University of Florence and Meyer Children's Hospital, Florence, Italy.

Drs. Prisco, Vaglio, and Emmi contributed equally to this work.

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Address correspondence to Giacomo Emmi, MD, PhD, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy. Email: giacomo.emmi@unifi.it.

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prednisone dose (or equivalent) of ≤4.0 mg/day, as defined by the MIRRA trial (11). Partial response to treatment was defined as no disease activity and a prednisolone or prednisone dose of >4.0 mg/day.

Relapse was assessed only in patients in whom complete response to treatment had been achieved and was defined, as in the MIRRA trial, by at least 1 of the following criteria: 1) active vasculitis (defined as BVAS >0) and/or 2) worsening asthma and/or ENT manifestations leading to an increase in prednisolone or prednisone dose to >4.0 mg/day, initiation of a new immunosuppressive therapy, or hospitalization (11).

With regard to respiratory outcomes, we assessed asthma exacerbations, defined as any of the following events: asthma attack needing an increase in oral prednisone dose, asthma-related emergency department admission, and/or use of acute oral glucocorticoids, antibiotics, or short-acting beta agonists. In addition, the effect of mepolizumab on lung function was monitored by the variation in pre-bronchodilator forced expiratory volume in 1 second (FEV_1). ENT relapse was defined as the reappearance of ENT symptoms, following symptoms having been under complete control at the previous time point.

Additional outcomes assessed included changes in organ manifestations (assessed separately from BVAS items), glucocorticoid-sparing and disease-modifying antirheumatic drug (DMARD)–sparing effect, variation in the proportion of ANCA-positive patients, and reduction in eosinophil count.

During follow-up, variations in monthly mepolizumab dose or treatment discontinuation were recorded. All adverse events (AEs) occurring during treatment were also recorded, and their seriousness was assessed in accordance with the World Health Organization criteria (19). All study outcome measures were analyzed in the entire cohort and compared between patients receiving stable treatment with mepolizumab 100 mg every 4 weeks and those treated with 300 mg every 4 weeks. Stable treatment was defined as no change in the monthly mepolizumab dose during the entire follow-up period.

Statistical analysis. Data are presented as the median and interquartile range (IQR) for continuous variables, and as the absolute number and percentage for qualitative variables. Continuous end points at 3–24 months were compared with time 0 (baseline) using the Wilcoxon signed rank test, whereas qualitative variables were compared using McNemar's test. Nonparametric tests were used since the distribution of the data was not normal. Complete response and partial response rates and AE rates were compared between patients receiving stable treatment with mepolizumab 100 mg every 4 weeks and those receiving 300 mg every 4 weeks using Fisher's exact test. Cox proportional hazards regression models were fitted to derive Kaplan–Meier curves and to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the occurrence of asthma and ENT exacerbations over time.

If a patient was still receiving mepolizumab treatment at a given follow-up time point but had missing data regarding EGPA manifestations, BVAS score, and/or daily glucocorticoid dose, the data were imputed using the last observation carried forward method, as these parameters were necessary to assess the primary outcome measure of this study. For all other clinical and laboratory parameters, the analyses were conducted only on subjects with available data at the given time point.

Statistical analyses were performed using Stata, version 14. *P* values less than 0.05 were considered significant.

Data availability. Deidentified individual participant data will be made available upon reasonable request to the corresponding author.

RESULTS

We included 203 patients, of whom 57.1% were women (Table 1). The median age at the time of mepolizumab initiation was 55.1 years (IQR 46.7–62.5), and the median disease duration was 4.8 years (IQR 4.9–9.2). At the time of EGPA diagnosis, 70 patients (34.5%) were positive for ANCAs, most of whom had either perinuclear ANCAs or myeloperoxidase ANCAs (84.3%). Before mepolizumab treatment was initiated, 150 of 203 patients (73.9%) had received traditional DMARDs, 51 (25.1%) received biologic DMARDs, and 18 (9.0%) received intravenous immunoglobulin. Disease remission, according to clinical judgment, was achieved in 120 patients after induction therapy. At the time of mepolizumab initiation (baseline), 92.1% of the patients had active disease, with a median BVAS score of 4 (IQR 2–8). The most common manifestations were pulmonary (89.7%), ENT (71.4%), constitutional (27.6%), and peripheral neurologic (22.7%). Ten patients had cardiac involvement at baseline, including 1 case of pericarditis, 1 case of myocarditis, and 8 cases of cardiomyopathy with cardiac failure. Of 190 patients with available ANCA test results, 38 (20.0%) were ANCA positive at the time mepolizumab was initiated, most of whom had perinuclear ANCAs or myeloperoxidase-ANCAs (89.5%). At baseline, almost all patients (95.6%) had received stable glucocorticoid treatment in the previous 3 months, at a median prednisone dose of 10 mg/day (IQR 5–20). Additional therapies included conventional DMARDs, mostly methotrexate (18.7%), azathioprine (11.3%), rituximab (11.3%), or intravenous immunoglobulin (5.9%). One hundred ninety-two patients (95%) were receiving inhaled therapy for asthma.

One hundred sixty-eight patients initially received mepolizumab at 100 mg every 4 weeks, and 35 at 300 mg every 4 weeks. During follow-up, 10 patients switched from 100 mg to 300 mg every 4 weeks due to inefficacy. Another 2 patients switched from 300 mg to 100 mg every 4 weeks due to personal reasons (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.

Table 1. Characteristics of the patients with EGPA at the time of mepolizumab initiation*

	Overall (n = 203)	Mepolizumab 100 mg/4 weeks (n = 158)	Mepolizumab 300 mg/4 weeks (n = 33)	*P*
Female	116 (57.1)	88 (55.7)	22 (66.7)	0.333
Smoking status				
Former	44 (21.7)	36 (22.8)	5 (15.2)	0.640
Current	3 (1.5)	3 (1.9)	0	
Age at diagnosis, median (IQR) years	49.1 (37.7–57.1)	48.7 (37.9–57.5)	49.2 (39.8–53.4)	0.380
Age at mepolizumab initiation, median (IQR) years	55.1 (46.7–62.5)	55.1 (46.7–62.8)	53.0 (47.3–59.3)	0.426
Disease duration at mepolizumab initiation, median (IQR) years	4.8 (4.9–9.2)	4.9 (1.6–8.9)	3.9 (1.1–14.1)	0.921
Active organ involvement at mepolizumab initiation				
Constitutional	56 (27.6)	50 (31.7)	3 (9.1)	0.009
Purpura	15 (7.4)	11 (7.0)	2 (6.1)	1.000
ENT	145 (71.4)	121 (76.6)	17 (51.5)	0.005
Pulmonary	182 (89.7)	141 (89.2)	29 (87.9)	0.765
Cardiac	10 (4.9)	8 (5.1)	1 (3.0)	1.000
Gastrointestinal	9 (4.4)	8 (5.1)	1 (3.0)	1.000
Renal	5 (2.5)	5 (3.2)	0	NA
Peripheral neurologic	46 (22.7)	36 (22.8)	6 (18.2)	0.650
Active disease at mepolizumab initiation (BVAS >0)	187 (92.1)	144 (91.1)	31 (93.9)	0.792
BVAS score at mepolizumab initiation, median (IQR)	4 (2–8)	4 (2–8)	4 (2–7)	0.163
Laboratory parameters at mepolizumab initiation†				
ANCA positive	38 (20.0)	28 (18.9)	9 (27.3)	0.339
Perinuclear ANCA	34 (17.9)	26 (17.6)	8 (24.2)	
Cytoplasmic ANCA	4 (2.1)	2 (1.4)	1 (3.0)	
MPO ANCA	34 (17.9)	27 (18.2)	8 (24.2)	
PR3 ANCA	4 (2.1)	2 (1.4)	1 (3.0)	
Eosinophil count, median (IQR)‡	610 (200–1,040)	700 (200–1,080)	440 (200–910)	0.328
Pharmacologic therapies administered before mepolizumab initiation				
Oral glucocorticoids	201 (99.0)	156 (98.7)	33 (100.0)	NA
Azathioprine	91 (44.8)	69 (43.7)	17 (51.5)	0.446
Methotrexate	78 (38.4)	56 (35.4)	18 (54.6)	0.050
Cyclophosphamide	57 (28.1)	44 (27.9)	11 (33.3)	0.531
Mycophenolate	39 (19.2)	29 (18.4)	6 (18.2)	1.000
Cyclosporine	21 (10.3)	18 (11.4)	1 (3.0)	0.206
Rituximab	39 (19.2)	36 (22.8)	3 (9.1)	0.097
IV immunoglobulin	18 (8.9)	17 (10.8)	1 (3.0)	0.321
Omalizumab	17 (8.4)	13 (8.2)	2 (6.1)	1.000
Other immunosuppressants	16 (7.9)	13 (8.2)	1 (3.0)	0.471
Pharmacologic therapies at mepolizumab initiation				
Prednisone equivalent daily dose in the previous 3 months, median (IQR)§	10 (5–20)	10 (IQR 5-20)	10 (IQR 5-22.5)	0.854
Oral glucocorticoids	194 (95.6)	149 (94.3)	33 (100.0)	NA
Prednisone equivalent daily dose, median (IQR)	10 (5–20)	10 (5–20)	10 (5–25)	0.511
Methotrexate	38 (18.7)	29 (18.4)	9 (27.3)	0.240
Azathioprine	23 (11.3)	19 (12.0)	3 (9.1)	0.772
Mycophenolate	18 (8.9)	12 (7.6)	4 (12.1)	0.486
Cyclosporine	2 (1.0)	1 (0.6)	0	NA
Rituximab	23 (11.3)	20 (12.7)	3 (9.1)	0.771
IV immunoglobulin	12 (5.9)	11 (7.0)	1 (3.0)	0.695
Other immunosuppressants	5 (2.5)	3 (1.9)	1 (3.0)	0.535
Inhaled therapy for asthma	192 (95.0)	150 (94.9)	30 (90.9)	0.407

* Except where indicated otherwise, values are the number (%). EGPA = eosinophilic granulomatosis with polyangiitis; IQR = interquartile range; ENT = ear, nose, and throat; NA = not applicable; BVAS = Birmingham Vasculitis Activity Score; ANCA = antineutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3; IV = intravenous.
† Data were available for 190 patients overall, 148 patients receiving mepolizumab 100 mg/4 weeks, and 33 patients receiving mepolizumab 300 mg/4 weeks.
‡ Data were available for 194 patients overall, 152 patients receiving mepolizumab 100 mg/4 weeks, and 32 patients receiving mepolizumab 300 mg/4 weeks.
§ Data were available for 195 patients overall, 151 patients receiving mepolizumab 100 mg/4 weeks, and 32 patients receiving mepolizumab 300 mg/4 weeks.

41943). Conversely, in 158 patients (77.8%) and 33 patients (16.3%), stable treatment with mepolizumab of 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, was maintained over the entire follow-up period.

Baseline demographic and clinical characteristics were comparable between these 2 groups, with the exception of constitutional and ENT manifestations, which were more frequent among patients receiving mepolizumab 100 mg every 4 weeks than those receiving 300 mg every 4 weeks (31.7% versus 9.1% [$P = 0.009$] and 76.6% versus 51.5% [$P = 0.005$], respectively) (Table 1).

Effectiveness of mepolizumab on systemic disease activity. At 3 months, complete response to treatment had already been achieved in 25 of 203 patients (12.3%), whereas partial response to treatment had been achieved in 64 patients (31.5%) (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Complete response rates increased to 23.6% at 6 months, 30.4% at 12 months, and 35.7% at 24 months. Response rates were similar between patients receiving mepolizumab 100 mg every 4 weeks and those receiving 300 mg every 4 weeks (Figure 1). In particular, complete response to treatment had been achieved in 12.0% and 18.2% of patients receiving 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, at 3 months, whereas partial response to treatment had been achieved in 32.9% and 36.4% of patients receiving 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, at 3 months ($P = 0.474$). Complete response rates further increased during follow-up for both treatment groups ($P = 0.204$ and $P = 0.809$ for mepolizumab 100 mg versus 300 mg every 4 weeks at 6 months and 12 months, respectively). At 24 months, only 39 patients receiving mepolizumab 100 mg every 4 weeks and 12 patients receiving 300 mg every 4 weeks had available follow-up data. A greater proportion of patients receiving mepolizumab 300 mg every 4 weeks had complete response to treatment (58.3% versus 33.3%) or partial response to treatment

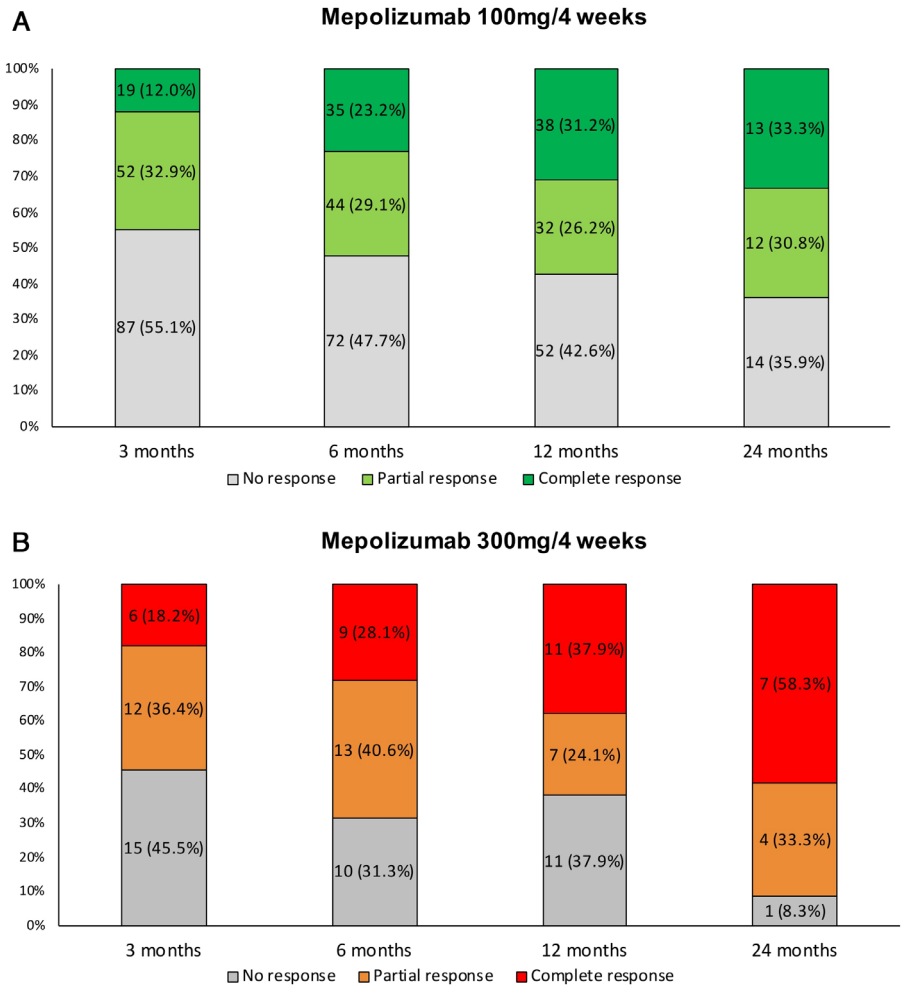
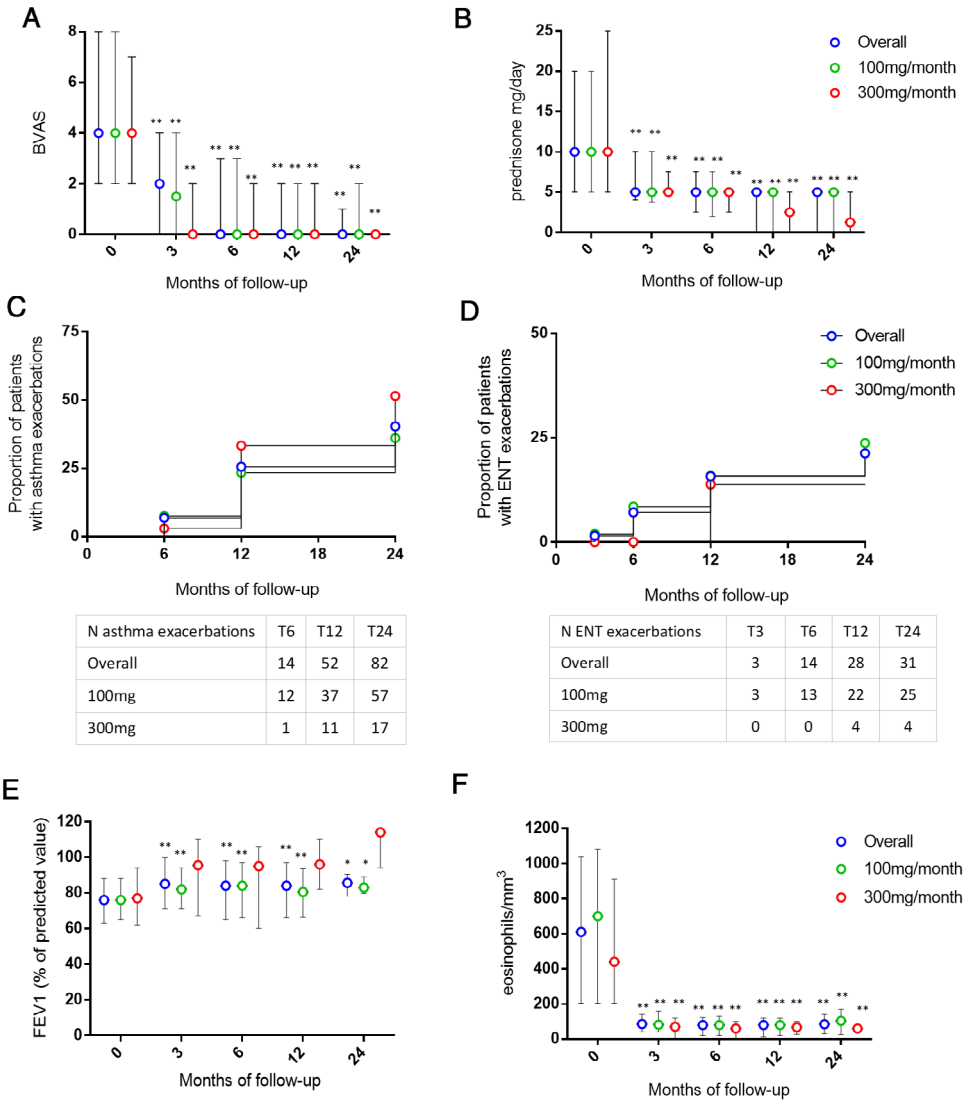


Figure 1. Complete and partial response rates in patients with eosinophilic granulomatosis with polyangiitis who received stable treatment with mepolizumab 100 mg every 4 weeks (**A**) and 300 mg every 4 weeks (**B**). Complete response was defined as no disease activity (Birmingham Vasculitis Activity Score [BVAS] = 0) and daily prednisone dose ≤4 mg/day. Partial response was defined as no disease activity (BVAS = 0) and daily prednisone dose >4 mg/day. No response was defined as active disease (BVAS >0).

Table 2. Organ involvement among the patients with EGPA receiving stable treatment with mepolizumab 100 mg or 300 mg every 4 weeks*

	Mepolizumab initiation (baseline) (n = 158/33)	3 months (n = 158/33)	*P*, 3 months vs. baseline	6 months (n = 151/32)	*P*, 6 months vs. baseline	12 months (n = 122/29)	*P*, 12 months vs. baseline	24 months (n = 39/12)	*P*, 24 months vs. baseline
Constitutional symptoms									
100 mg/4 weeks	50 (31.7)	25 (15.8)	<0.001	23 (15.2)	<0.001	15 (12.3)	<0.001	6 (15.4)	0.035
300 mg/4 weeks	3 (9.1)	0	NA	2 (6.3)	0.564	2 (6.9)	1.564	0	NA
Purpura									
100 mg/4 weeks	11 (7.0)	6 (3.8)	0.025	4 (2.7)	0.014	3 (2.5)	0.008	0	NA
300 mg/4 weeks	2 (6.1)	1 (3.0)	0.317	1 (3.1)	0.317	2 (6.9)	1.000	0	NA
ENT									
100 mg/4 weeks	121 (76.6)	64 (40.5)	<0.001	55 (36.4)	<0.001	34 (27.9)	<0.001	8 (20.5)	<0.001
300 mg/4 weeks	17 (51.5)	12 (36.4)	0.025	7 (21.9)	0.003	8 (27.6)	0.034	0	NA
Pulmonary									
100 mg/4 weeks	141 (89.2)	61 (38.6)	<0.001	46 (30.5)	<0.001	37 (30.3)	<0.001	7 (18.0)	<0.001
300 mg/4 weeks	29 (87.9)	10 (30.3)	<0.001	5 (15.6)	<0.001	9 (31.0)	<0.001	1 (8.3)	0.005
Cardiac									
100 mg/4 weeks	8 (5.1)	4 (2.5)	0.046	4 (2.7)	0.046	3 (2.5)	0.046	1 (2.6)	0.317
300 mg/4 weeks	1 (3.0)	0	NA	0	NA	0	NA	0	NA
Gastrointestinal									
100 mg/4 weeks	8 (5.1)	0	0.005	5 (3.3)	0.257	4 (3.3)	0.257	0	0.083
300 mg/4 weeks	1 (3.0)	1 (3.0)	NA	0	NA	0	NA	0	NA
Renal									
100 mg/4 weeks	5 (3.2)	1 (0.6)	0.046	0	NA	1 (0.8)	0.180	0	0.317
300 mg/4 weeks	0	2 (6.1)	0.157	0	NA	1 (3.5)	0.317	0	NA
Peripheral neurologic									
100 mg/4 weeks	36 (22.8)	23 (14.6)	0.005	21 (13.9)	0.001	15 (12.3)	0.001	2 (5.1)	0.005
300 mg/4 weeks	6 (18.2)	6 (18.2)	NA	3 (9.4)	0.157	2 (6.9)	0.157	0	NA

* Except where indicated otherwise, values are the number (%); n values are the number of patients receiving mepolizumab 100 mg every 4 weeks/number of patients receiving mepolizumab 300 mg every 4 weeks. EGPA = eosinophilic granulomatosis with polyangiitis; NA = not applicable; ENT = ears, nose, and throat.



N asthma exacerbations	T6	T12	T24
Overall	14	52	82
100mg	12	37	57
300mg	1	11	17

N ENT exacerbations	T3	T6	T12	T24
Overall	3	14	28	31
100mg	3	13	22	25
300mg	0	0	4	4

Figure 2. **A** and **B,** Variation in disease activity using the Birmingham Vasculitis Activity Score (BVAS) (**A**) and daily dose of prednisone equivalents (**B**) among patients with eosinophilic granulomatosis with polyangiitis receiving mepolizumab 100 mg every 4 weeks and those receiving mepolizumab 300 mg every 4 weeks. **C** and **D,** Respiratory outcomes in patients during mepolizumab treatment. Kaplan–Meier curves show the occurrence of asthma exacerbations (**C**) and ear, nose, and throat (ENT) exacerbations (**D**). **E** and **F**, Variation in the forced expiratory volume in 1 second (FEV_1) (**E**) and eosinophil count (**F**). Values in **A**, **B**, **E**, and **F** are the median and interquartile range.* = $P < 0.05$; ** = $P < 0.01$, versus baseline.

(33.3% versus 30.8%), but these differences were not statistically significant ($P = 0.168$). Notably, the small number of patients at the different follow-up time points, particularly those receiving mepolizumab 300 mg every 4 weeks, did not allow sufficient power to detect significant differences in the proportion of complete responses between the 2 doses at the different time points (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943).

Of 71 patients in whom complete response to treatment had been achieved, 22 (31.0%) experienced a relapse after a median time of 6 months (IQR 6–9). At all time points, relapse rates were comparable between both treatment groups ($P = 1.000$ at 6 months and 12 months; $P = 0.642$ at 24 months), the overall relapse rates being 32.1% (17 of 53) and 25.0% (4 of 16) for mepolizumab 100 versus 300 mg every 4 weeks, respectively. The median time to relapse was 6 months (IQR 3–9) and 10 months (IQR 9–12) in the mepolizumab 100 mg every 4 weeks group compared to the 300 mg every 4 weeks group, respectively ($P = 0.081$). Response rates were higher among ANCA-negative patients, especially at 24 months, but the differences were not statistically significant (Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943).

The efficacy outcomes in the 10 patients who switched from mepolizumab 100 mg every 4 weeks to 300 mg every 4 weeks are summarized in Supplementary Figure 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Follow-up data suggested

Table 3. AEs in the patients with EGPA during mepolizumab treatment*

	0–3 months	4–6 months	7–12 months	13–24 months
At least 1 AE experienced, no. of patients/total no. of patients (%)	21/203 (10.3)	20/195 (10.3)	16/161 (9.9)	9/56 (16.1)
Receiving stable treatment with mepolizumab 100 mg/4 weeks	10/158 (6.3)	13/151 (8.6)	6/122 (4.9)	3/39 (7.7)
Receiving stable treatment with mepolizumab 300 mg/4 weeks	9/33 (27.3)	5/32 (15.6)	10/29 (34.5)	6/12 (50.5)
P	<0.001	0.322	<0.001	0.003
No. of patients with AEs requiring hospitalization	0	2	2	2
Receiving stable treatment with mepolizumab 100 mg/4 weeks	0	1	2	1
Receiving stable treatment with mepolizumab 300 mg/4 weeks	0	1	0	1
AEs requiring treatment discontinuation	2	3	1	0
Receiving stable treatment with mepolizumab 100 mg/4 weeks	2	3	1	0
Receiving stable treatment with mepolizumab 300 mg/4 weeks	0	0	0	0
Type of AE and no. of cases				
Infections and infestations				
Lower respiratory tract infections	4	3†	7†	2
Upper respiratory tract infections	2	–	–	1
Other infections	–	2†	1	1
Musculoskeletal and connective tissue disorders				
Myalgia/arthralgia	3	1	1	–
Osteoporosis/fractures	1	1	1	1
Epicondylitis	–	1	–	–
Nervous system disorders				
Dizziness	1	–	1	–
Headache	2	1	–	–
Transient color vision disorder	–	1	–	–
Skin and subcutaneous tissue disorders				
Eczema/urticaria	2	1	–	–
Papillary edema	–	–	1	–
General disorders and administration site conditions				
Malaise	2	–	–	–
Swelling at injection site	1	–	–	–
Endocrine disorders				
Secondary adrenal insufficiency	–	–	–	1†
Blood and lymphatic system disorders				
Sialoadenitis	–	1	–	–
Cardiac disorders				
Myocarditis	–	–	–	1†
Hepatobiliary disorders				
Acute hepatitis	–	–	1	–
Renal and urinary disorders				
Renal colic	–	1	–	–
Respiratory, thoracic, and mediastinal disorders				
Lung consolidation	–	–	1	–
Vascular disorders				
TIA	–	–	1†	–

* AEs = adverse events; EGPA = eosinophilic granulomatosis with polyangiitis; TIA = transient ischemic attack.
† Hospitalization required in 1 patient.

no clear benefit in terms of EGPA control following the increase in monthly mepolizumab dose.

The impact of mepolizumab on the different disease manifestations is summarized in Table 2 and in Supplementary Table 4 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943). A significant reduction in all active manifestations was already observed at 3 months in patients receiving stable mepolizumab 100 mg every 4 weeks. Control of constitutional, pulmonary, ENT, and peripheral neurologic manifestations was maintained during follow-up. With mepolizumab 300 mg every 4 weeks, a significant reduction in the proportion of patients with pulmonary and ENT manifestations was observed at all time points, whereas no clear effect was observed on nonrespiratory manifestations.

Systemic disease activity also decreased during follow-up for both treatment groups, with the median BVAS score of the entire

cohort decreasing from 4 (IQR 2–8) at baseline to 2 (IQR 0–4) at 3 months ($P < 0.001$). The median BVAS score decreased further to 0 at the subsequent time points ($P < 0.001$ for both treatment groups at 6 months, 12 months, and 24 months) (Figure 2A). Similarly, both mepolizumab doses were associated with a significant reduction in the daily glucocorticoid dose (Figure 2B), with a significant proportion of patients able to discontinue glucocorticoid use (29.2% and 41.7% at 24 months in the 100 mg mepolizumab group and the 300 mg mepolizumab group, respectively) (Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Concomitantly, a DMARD-sparing effect was observed in both treatment groups, though statistical significance was only achieved for mepolizumab 100 mg every 4 weeks (Supplementary Table 5).

Effectiveness of mepolizumab on respiratory outcomes. Respiratory outcomes are reported in Figures 2C–F and in Supplementary Table 6 (http://onlinelibrary.wiley.com/doi/10.1002/art.41943). Overall, 82 patients (40.4%) experienced asthma exacerbations after a median time of 12 months (IQR 12–24). Asthma exacerbations occurred in 36.1% of patients receiving stable mepolizumab 100 mg every 4 weeks and in 51.5% receiving mepolizumab 300 mg every 4 weeks ($P = 0.139$) (Figure 2C). ENT relapses occurred after a median time of 12 months (IQR 6–12) in 25 patients receiving mepolizumab 100 mg every 4 weeks (15.8%), 4 receiving 300 mg every 4 weeks (12.2%), and 2 who switched mepolizumab dose (unadjusted HR 0.67 [95% CI 0.23–1.91] for mepolizumab 300 mg every 4 weeks versus 100 mg every 4 weeks, $P = 0.450$) (Figure 2D).

With regard to lung function, a significant improvement in FEV_1 was already observed 3 months after the initiation of mepolizumab 100 mg every 4 weeks (Figure 2E). FEV_1 also improved in patients receiving mepolizumab 300 mg every 4 weeks, though statistical significance was not reached.

Additional outcomes. Both mepolizumab regimens were already associated with a dramatic reduction in eosinophil count at 3 months. This was maintained during the entire follow-up period (Figure 2F). Although ANCA testing was available for only a small subgroup of patients during follow-up, a significant reduction in the proportion of ANCA-positive patients was observed among those receiving stable mepolizumab 100 mg every 4 weeks and those receiving 300 mg every 4 weeks (Supplementary Figure 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41943).

Treatment persistence and safety. Twenty-three patients discontinued mepolizumab. Sixteen of these patients were receiving mepolizumab 100 mg every 4 weeks; reasons for discontinuation were AEs in 6 cases (malaise in 2 patients, arthralgia in 1, reactivation of herpes zoster in 1, and not reported in 2) and inefficacy in 3 cases. In the remaining 7 patients, the reason for treatment discontinuation was unknown. Seven patients discontinued mepolizumab 300 mg every 4 weeks due to inefficacy (4 patients) and unknown reasons (3 patients).

Forty-four patients (21.7%) experienced AEs, mostly related to lower respiratory tract infections or to myalgias or arthralgias. At all time points, AEs were more frequent among patients receiving mepolizumab 300 mg every 4 weeks (Table 3). Overall, 6 AEs required hospitalization, of which 4 occurred in patients receiving mepolizumab 100 mg every 4 weeks (lower respiratory tract infection, secondary adrenal insufficiency, transient ischemic attack, and infection of the central venous catheter). The other 2 AEs occurred in patients receiving mepolizumab 300 mg every 4 weeks (lower respiratory tract infection and myocarditis).

DISCUSSION

In this study, conducted on the largest series of mepolizumab-treated patients with EGPA reported so far to our knowledge, we observed that mepolizumab at either 100 mg every 4 weeks or 300 mg every 4 weeks is effective and safe in controlling systemic and respiratory disease manifestations. The use of mepolizumab in EGPA has solid evidence. Indeed, the randomized controlled MIRRA trial proved the superiority of mepolizumab 300 mg every 4 weeks compared to placebo for relapsing and/or refractory EGPA (11,12), leading to the FDA approval of mepolizumab 300 mg every 4 weeks.

Despite this, our data show that, in real practice, most patients with EGPA received mepolizumab 100 mg every 4 weeks, the dose approved for severe eosinophilic asthma, rather than 300 mg every 4 weeks. This prescription was probably based on the rationale that mepolizumab 100 mg every 4 weeks effectively controls severe eosinophilic asthma, which is an invariable feature of EGPA, and was also driven by regulatory reasons, since mepolizumab 300 mg every 4 weeks is not currently approved in Europe.

In the MIRRA trial, the dose choice was based on the phase IIb/III dose range–finding study of mepolizumab in severe eosinophilic asthma (7), and in a trial of HES (20,21). This choice was also supported by the concept that EGPA, similarly to HES, is a more aggressive condition compared to eosinophilic asthma (14). After the FDA approval of mepolizumab 300 mg every 4 weeks for EGPA, a growing body of literature from real clinical practice suggested that mepolizumab 100 mg every 4 weeks might also be used for EGPA (13–15,22). Notably, in all patients included in these studies, disease was in remission (13,15) or disease activity was low (14) at treatment initiation, with mepolizumab being initiated mainly for the control of asthma.

Our results indicate that mepolizumab at both 100 mg every 4 weeks and 300 mg every 4 weeks was associated with effective control of respiratory EGPA manifestations and an improvement in systemic disease activity. Both also allowed glucocorticoid-sparing.

Also, the proportion of ANCA-positive patients significantly decreased unexpectedly; nevertheless, given the small number of patients with ANCA (re)testing, this finding should be interpreted with caution. Though the exact mechanisms of ANCA positivity-to-negativity switch are unknown, this may be accounted for by anti–IL-5–mediated eosinophil depletion. Eosinophils have been shown to promote B cell survival, T-independent and T-dependent B cell activation and proliferation, and immunoglobulin secretion (23). B cells and their progeny produce and release ANCAs; thus, eosinophil depletion following mepolizumab treatment may account for the reduction in antigen presentation and plasma cell survival, with a consequent reduction in ANCA titers.

The proportion of complete responses steadily increased throughout follow-up, reaching 31.2% and 37.9% at 12 months and 33.3% and 58.3% at 24 months for mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, with only a small proportion of patients experiencing disease relapse. However, response rates at 24 months must be interpreted with caution, as only 39 patients receiving mepolizumab 100 mg every 4 weeks and 12 patients receiving 300 mg every 4 weeks had available follow-up data. Notably, complete response rates observed with both doses were similar to that reported in the MIRRA trial for mepolizumab 300 mg every 4 weeks, where complete response to treatment was achieved in 32% of patients at both weeks 36 and 48 (11). The response rates in our study were lower than those in the observational study by Canzian et al (14) in a small EGPA cohort (76% and 82% complete responses at 12 months for mepolizumab 100 mg every 4 weeks and 300 mg every 4 weeks, respectively, as defined by BVAS = 0 and a prednisone dose ≤5 mg/day) (14).

In our study, complete response rates appeared to be higher among ANCA-negative patients, though the subgroups were too small to draw conclusions. We speculate that these findings reflect the different nature of ANCA-positive EGPA and ANCA-negative EGPA, the latter being traditionally associated with a more prominent eosinophilic phenotype (24–26).

Control of systemic disease activity was paralleled by the improvement in asthma and lung function with both mepolizumab regimens. Interestingly, the lower mepolizumab dose was not associated with an increased risk of asthma re-exacerbation during follow-up. Additionally, both mepolizumab doses were associated with good control of ENT manifestations, according to recent data (27). Moreover, we also observed a remarkable reduction in peripheral neuropathy during treatment with mepolizumab. In EGPA, neuropathy seems to have not only a vasculitic etiology but also a neurotoxic etiology, mainly due to eosinophil products (28,29). Thus, eosinophil depletion via mepolizumab could effectively counteract this pathogenetic mechanism. To date, the possible role of mepolizumab in the control of EGPA neurologic manifestations was reported only in a retrospective study of 6 patients (30). Our results, however, must be taken with caution, as other factors may contribute to the improvement of neuropathy, including progressive nerve function recovery or delayed effects of previous and concomitant therapies.

In our study, mepolizumab was generally well-tolerated. Approximately one-fifth of patients experienced AEs, and the 100 mg every 4 weeks dose appeared to be associated with a lower rate of AEs. Most AEs were related to infections or to myalgias/arthralgias, as observed in the MIRRA trial (11). Only a few AEs required treatment discontinuation or hospitalization. However, as is the case in all retrospective studies, underreporting of AEs cannot be excluded.

Our study has other limitations, mostly related to its retrospective nature. First, as data were retrospectively captured from medical records, some data were missing, and the assessment of clinical parameters was not systematic. Second, heterogeneity in clinical management among centers cannot be excluded. Third, consistent with the MIRRA trial, the BVAS calculation was used to retrospectively assess disease activity and treatment outcomes, as no standard assessment tool is validated specifically for EGPA. Nevertheless, it cannot be excluded that items related to chronic or persistent damage were erroneously counted in the BVAS score. Fourth, the disparity in sample size between the 100 mg every 4 weeks group and 300 mg every 4 weeks group did not allow us to draw definite conclusions. Finally, given the small sample size, the effect of mepolizumab dose escalation in patients with inappropriate response to 100 mg every 4 weeks could not be ascertained. Despite these limitations, this study also had several strengths, including a long follow-up period, large sample size representative of the European clinical setting, and availability of detailed longitudinal clinical data.

In conclusion, this large European real-world study shows that mepolizumab is associated with effective control of respiratory EGPA manifestations, with a good safety profile. Our results further suggest a role of mepolizumab in the treatment of systemic manifestations, though the retrospective assessment of systemic disease activity requires cautious interpretation of these findings.

Our data also suggest that mepolizumab 100 mg every 4 weeks could be an acceptable dose for patients with EGPA and a valid alternative to the dose approved for this therapeutic indication (300 mg every 4 weeks). Nevertheless, caution is needed, as some reports suggest a risk of systemic disease flare in patients receiving anti–IL-5 treatments at the dose for asthma control (31,32). Randomized clinical trials are advocated to compare the efficacy and safety of these 2 EGPA treatment regimens and assess whether dose escalation from 100 mg to 300 mg every 4 weeks can be effective in case of unsatisfactory clinical responses, as well as to compare the efficacy of mepolizumab as an alternative to or sequential treatment with other biologic therapies for EGPA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bettiol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bettiol, Urban, Prisco, Vaglio, Emmi.

Acquisition of data. Dagna, Cottin, Franceschini, Del Giacco, Schiavon, Neumann, Lopalco, Novikov, Baldini, Lombardi, Berti, Alberici, Folci, Negrini, Sinico, Quartuccio, Lunardi, Parronchi, Moosig, Espígol-Frigolé, Schroeder, Kernder, Monti, Silvagni, Crimi, Cinetto, Fraticelli, Roccatello, Vacca, Mohammad, Hellmich, Samson, Bargagli, Cohen Tervaert, Ribi, Fiori, Bello, Fagni, Moroni, Ramirez, Nasser, Marvisi, Toniati, Firinu, Padoan, Egan, Seeliger, Iannone, Salvarani, Jayne.

Analysis and interpretation of data. Bettiol, Urban, Salvarani, Jayne, Prisco, Vaglio, Emmi.

REFERENCES

1. Trivioli G, Terrier B, Vaglio A. Eosinophilic granulomatosis with polyangiitis: understanding the disease and its management [review] Rheumatology (Oxford) 2020;59:iii84–94.
2. Bettiol A, Sinico RA, Schiavon F, Monti S, Bozzolo EP, Franceschini F, et al. Risk of acute arterial and venous thromboembolic events in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Eur Respir J 2021;57:2004158.
3. Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, et al. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015;26:545–53.
4. Emmi G, Rossi GM, Urban ML, Silvestri E, Prisco D, Goldoni M, et al. Scheduled rituximab maintenance reduces relapse rate in eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis 2017;77:952–4.
5. Fagni F, Bello F, Emmi G. Eosinophilic granulomatosis with polyangiitis: dissecting the pathophysiology [review]. Front Med 2021;8:267776.
6. Lyons PA, Peters JE, Alberici F, Liley J, Coulson RM, Astle W, et al. Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. Nat Commun 2019;10:5120.
7. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651–9.
8. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;146:1397–405.
9. Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome. Clin Exp Rheumatol 2012;30:S62–5.
10. Moosig F, Gross WL, Herrmann K, Bremer JP, Hellmich B. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. Ann Intern Med 2011;155:341.
11. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 2017;376:1921–32.
12. Steinfeld J, Bradford ES, Brown J, Mallett S, Yancey SW, Akuthota P, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol 2019;143:2170–7.
13. Vultaggio A, Nencini F, Bormioli S, Vivarelli E, Dies L, Rossi O, et al. Low-dose mepolizumab effectiveness in patients suffering from eosinophilic granulomatosis with polyangiitis. Allergy Asthma Immunol Res 2020;12:885–93.
14. Canzian A, Venhoff N, Urban ML, Sartorelli S, Ruppert A, Groh M, et al. Use of biologics to treat relapsing and/or refractory eosinophilic granulomatosis with polyangiitis: data from a European collaborative study. Arthritis Rheumatol 2020;73:498–503.
15. Caminati M, Crisafulli E, Lunardi C, Micheletto C, Festi G, Maule M, et al. Mepolizumab 100 mg in severe asthmatic patients with EGPA in remission phase. J Allergy Clin Immunol Pract 2020;9:1386–8.
16. Faverio P, Bonaiti G, Bini F, Vaghi A, Pesci A. Mepolizumab as the first targeted treatment for eosinophilic granulomatosis with polyangiitis: a review of current evidence and potential place in therapy. Ther Clin Risk Manag 2018;14:2385–96.
17. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094–100.
18. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827–32.
19. European Medicines Agency. ICH Topic E 2 A. Clinical safety data management: definitions and standards for expedited reporting. 1995. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-15.pdf.
20. Moiseev S, Zagvozdkina E, Kazarina V, Bulanov N, Novikov P. Mepolizumab in patients with eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol 2019;144:621.
21. Roufosse FE, Kahn JE, Gleich GJ, Schwartz LB, Singh AD, Rosenwasser LJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. J Allergy Clin Immunol 2013;131:461–7.
22. Thompson G, Vasilevski N, Ryan M, Baltic S, Thompson P. Low-dose mepolizumab effectively treats chronic relapsing eosinophilic granulomatosis with polyangiitis [abstract]. Australia and New Zealand Society of Respiratory Science and The Thoracic Society of Australia and New Zealand: Abstracts from the Annual Scientific Meeting in Adelaide, Australia, 23-27 March 2018. URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01607187/full.
23. Wong TW, Doyle AD, Lee JJ, Jelinek DF. Eosinophils regulate peripheral B cell numbers in both mice and humans. J Immunol 2014;192:3548–58.
24. Sablé-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 2005;143:632–8.
25. Papo M, Sinico RA, Teixeira V, Venhoff N, Urban ML, Iudici M, et al. Significance of PR3-ANCA positivity in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Rheumatology (Oxford) 2021;60:4355–60.
26. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013;65:270–81.
27. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps

(SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021;9:1141–53.
28. Khoury P, Grayson PC, Klion AD. Eosinophils in vasculitis: characteristics and roles in pathogenesis [review]. Nat Rev Rheumatol 2014; 10:474–83.
29. Kingham PJ, McLean WG, Walsh MT, Fryer AD, Gleich GJ, Costello RW. Effects of eosinophils on nerve cell morphology and development: the role of reactive oxygen species and p38 MAP kinase. Am J Physiol Lung Cell Mol Physiol 2003;285:L915–24.
30. Kitamura N, Hamaguchi M, Nishihara M, Ikumi N, Sugiyama K, Nagasawa Y, et al. The effects of mepolizumab on peripheral circulation and neurological symptoms in eosinophilic granulomatosis with polyangiitis (EGPA) patients. Allergol Int 2021;70:148–9.
31. Mukherjee M, Lim HF, Thomas S, Miller D, Kjarsgaard M, Tan B, et al. Airway autoimmune responses in severe eosinophilic asthma following low-dose Mepolizumab therapy. Allergy Asthma Clin Immunol 2017;13:2.
32. Caminati M, Menzella F, Guidolin L, Senna G. Targeting eosinophils: severe asthma and beyond [review]. Drugs Context 2019;8:212587.

APPENDIX A: EUROPEAN EGPA STUDY GROUP

Members of the EGPA Study Group are as follows: Kais Ahmad (Hospices Civils de Lyon, Lyon, France), Mirko Beccalli (IRCCS Ospedale Policlinico San Martino, Genoa, Italy), Bernard Bonnotte (Dijon University Hospital, Dijon, France), Roberto Bortolotti (Santa Chiara Hospital, Trento, Italy), Adriana Cariddi (IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy), Marco Caminati (University of Verona, Italy), Maria C Cid (University of Barcelona; Institut d'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain), Margherita Deidda (University of Cagliari, Cagliari, Italy), Paolo Delvino (IRCCS Policlinico S. Matteo Fondazione, University of Pavia, Pavia, Italy), Gerardo Di Scala (University of Florence, Florence, Italy), Mara Felicetti (Azienda Ospedaliera-Universitaria di Padova, Padova, Italy), Francesco Ferro (University of Pisa, Pisa, Italy), Federica Furini (University of Ferrara, Ferrara, Italy), Elena Gelain (Meyer Children's University Hospital, Florence, Italy), Giulia Ghirelli (University Hospital "Ospedali Riuniti," Ancona, Foggia, Italy), Julia Holle (Rheumazentrum Schleswig-Holstein Mitte, Neumünster, Germany), Laura Michelina Losappio (ASST GOM Niguarda, Milan, Italy), Alfred Mahr (Cantonal Hospital St. Gallen, St. Gallen, Switzerland), Danilo Malandrino (University of Florence, Florence, Italy), Juliane Marhhold (Medius Kliniken, Kirchheim-Teck, Germany), Irene Mattioli (University of Florence, Florence, Italy), Laura Moi (University Hospital Center of Lausanne, Lausanne, Switzerland), Sergey Moiseev (Sechenov First Moscow State Medical University, Moscow, Russia), Francesco Muratore (Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy), Santi Nolasco (University of Catania, Catania, Italy), Bianca Olivieri (University of Verona, Verona, Italy), Adalgisa Palermo (University of Florence, Florence, Italy), Francesca Regola (University of Brescia, Brescia, Italy), Oliver Sander (Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany), Riccardo Scarpa (University of Padova, Padova, Italy), Savino Sciascia (San Giovanni Bosco Hospital and University of Turin, Turin, Italy), Elena Silvestri (University of Florence, Florence, Italy), Nicola Susca (University of Brescia, Brescia, Italy), Benjamin Terrier (University of Paris, Assistance Publique-Hôpitaux de Paris, Cochin Hospital, Paris, France), Elena Treppo (University of Udine, Udine, Italy), Barbara Trezzi (University of Milano Bicocca, Monza, Italy), Martina Uzzo (ASST Santi Paolo e Carlo, Milan, Italy; University of Milano, Milan, Italy), Gianfranco Vitiello (University of Florence, Florence, Italy), and Elaine Yacyshyn (University of Alberta, Edmonton, Alberta, Canada; Maastricht University, Maastricht, The Netherlands).

Clinical picture, outcomes, and predictors of relapse in eosinophilia-associated coronary vasospasm: Data from a European multicentric study

Florent Huang, MD[a,b,*], Lucas Rémi Khellaf, MD[b,*], Guillaume Lefèvre, MD, PhD[b,c,d], Alvise Berti, MD, PhD[e,f], Thomas d'Humières, MD, PhD[g], Alessandro Sionis, MD, PhD[h], Albert Ariza Solé, MD, PhD[i], Federica Bello, MD[j,k], Juan Andres Bermeo Garrido, MD[i], Etienne Crickx, MD, PhD[l], Paolo Delvino, MD[m,n], Giacomo Emmi, MD, PhD[j,k,o], Antoine Gaillet, MD[b,p], Gilles Garcia, MD, PhD[q], Pierre-Edouard Gavand, MD[r], Jean-Louis George, MD[s], Floriane Gilles, MD[s], Cécile Golden, MD[t], Pascal de Groote, MD[b,u,v], Aurélien Guffroy, MD, PhD[w], Nihal Martis, MD[x], Sara Monti, MD, PhD[m], Pierre Mourlanette, MD[y], Marc Pineton de Chambrun, MD, PhD[z], Fabrice Prunier, MD, PhD[aa], Francesca Regola, MD[ab], Gabriel Seret, MD[ac], Benjamin Terrier, MD, PhD[ad], Ludovic Tréfond, MD[ae], Géraud Souteyrand, MD, PhD[af], Olivier Varenne, MD, PhD[ac], Filippo Zilio, MD[ag], Franck Haziza, MD, MSc[a], Hakim Benamer, MD, MSc[a], Jean-Emmanuel Kahn, MD, Pha[b,ah], Alexandre Vallée, MD, PhD[ai], and Matthieu Groh, MD, MSc[b]; on behalf of the French National Reference Center for Hypereosinophilic Syndromes and European EGPA Study Groups

Clinical Implications

Eosinophilia-associated coronary vasospasm is a life-threatening condition that can occur even with mild eosinophilia and despite treatment with vasodilators, especially in patients with features of type 2 inflammation. Long-term normalization of absolute eosinophil counts is warranted to prevent relapses.

Eosinophilia-associated coronary vasospasm is an underrecognized condition that has been described in patients with aspirin-exacerbated respiratory disease (AERD), hypereosinophilic syndrome (HES), and eosinophilic granulomatosis with polyangiitis (EGPA).[1] In the acute phase, the treatment relies on vasodilators and glucocorticoids. Nevertheless, the optimal long-term management is unknown. We previously reported that benralizumab could be beneficial in recurrent eosinophilia-associated coronary vasospasms unresponsive to conventional vasodilators.[2] We aimed to set up the first cohort of patients with eosinophilia-associated coronary vasospasm to provide an in-depth analysis of their clinical picture and outcomes, and ultimately to yield a practical data-driven therapeutic algorithm.

Coronary vasoSPASM with EOsinophilia is a European, multicentric, retrospective cohort study conducted in 20 centers from the French National Network for HES and the European EGPA study group dedicated to patients with eosinophilia-associated coronary vasospasm managed between January 2010 and January 2023. Inclusion criteria were the presence of a definite coronary vasospasm according to the 2017 International standardization of diagnostic criteria for vasospastic angina,[3] concomitant (±48-hour) eosinophilia (absolute eosinophil count [AEC] threshold, 0.5×10^9/L), and the absence of alternate diagnoses. This study complied with the relevant regulations (including the MR004 legislation) and was approved by Foch Hospital's ethics committee (IRB00012437).

A total of 37 patients (median age, 52 years [range, 42-64 years]; 43% women) were included (Table I). The coronary vasospasm was the first eosinophil-associated organ involvement in 26 patients (70%). An iatrogenic trigger was evidenced in seven patients (19%), consisting in all cases but one of nonsteroidal anti-inflammatory drugs, most often in the context of AERD. A total of 16 patients (43%) had AERD, whereas 16 (43%) and 13 (35%) fulfilled classification criteria for EGPA (all with negative antineutrophil cytoplasmic antibodies) and HES, respectively. No predominant coronary territory was involved and up to 10 of 34 patients (29%) displayed multivessel vasospasms.

After a median follow-up of 30 months (range, 12-63 months), 20 patients relapsed (54%), with relapse rates at 1, 2, and 5 years of 32%, 38%, and 49%, respectively. Besides coronary relapses, 13 patients (35%) experienced another major adverse cardiovascular event, including eight with cardiogenic shock (22%) and six with cardiac arrests (17%). In patients who relapsed (among whom 95% were treated with vasodilators and 55% with a combination of both nitrates and calcium channel blockers), median time to the first relapse was 10 months (range, 5-29 months) and there was a median total of three relapses at last follow-up (range, 1-3 relapses). All patients but one who relapsed (95%) had persistent eosinophilia (median AEC at the time of relapse, 1.00 × 109/L [range, 0.78-1.55 $\times 10^9$/L]). Among patients who relapsed and were treated with corticosteroids after the first coronary vasospasm (n = 10), four relapsed after recent withdrawal (<6 months), and six when eosinophilia recurred along with the tapering of corticosteroids. Conversely, after a median follow-up of 44 months (range, 17-50 months), all six patients who were treated with either mepolizumab (n = 4) or benralizumab (n = 2) remained relapse-free (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In multivariate analysis, persistent eosinophilia (defined as an AEC of $>0.5 \times 10^9$/L either at the time of relapse or at follow-up for patients who did or did not relapse, respectively) was the only independent factor associated with relapse (odds ratio = 8.87 [range, 3.28-24.82]; $P < .001$). Relapse-free survival curves are reported in Figure 1.

Here, we show that eosinophilia-associated coronary vasospasm is a life-threatening condition that can occur even with mild eosinophilia, especially in patients with features of type 2 inflammation. When patients do not receive eosinophil-

TABLE I. Baseline characteristics, in-hospital features, management, and outcomes of 37 patients with eosinophilia-associated coronary vasospasm

Variable	All patients (n = 37)	Patients without vasospasm relapse (n = 17)	Patients with vasospasm relapse (n = 20)	*P*[a]
Demographics and medical history				
Age, y	52 [42-64]	56 [50-65]	47 [35-64]	.128
Women/men	16 (43)/21 (57)	4 (24)/13 (76)	12 (60)/8 (40)	**.026**
Cardiovascular risk factors, n	1 [1-2]	1 [0-2]	1 [0-2]	.798
Active smoker	15 (40.5)	7 (41)	8 (40)	.942
Prior coronary revascularization	4 (11)	3 (18)	1 (5)	.217
Aspirin-exacerbated respiratory disease	16 (43)	6 (35)	10 (50)	.368
Asthma	21 (57)	5 (29)	16 (80)	**.002**
Atopy	14 (38)	4 (24)	10 (50)	.098
Atopic dermatitis	8 (22)	4 (24)	4 (20)	.795
Chronic rhinosinusitis with nasal polyps	14 (38)	3 (18)	11 (55)	**.019**
Cardiovascular findings				
Provisional diagnosis of Prinzmetal angina	25 (68)	5 (29)	20 (100)	**<.001**
Time between onset of angina and hospitalization, d	2 [0-30]	1 [0-18]	4 [0-30]	.662
Drug intake as trigger of coronary vasospasm	7 (19)	6 (35)	1 (5)	**.019**
Nonsteroidal anti-inflammatory drugs	6/7 (86)	5/6 (83)	1/1 (100)	**.045**
Peak troponin during hospitalization, multiple of upper reference limit	4.0 [0.6-20.8]	4.0 [1.2-8.9]	3.1 [0.3-25.5]	.638
Left ventricular ejection fraction at admission (upon transthoracic echocardiogram) (%)	60 [55-60]	60 [55-60]	60 [55-60]	.753
Coronary angiography features	34 (92)	15 (88)	19 (95)	.453
Multivessel involvement	10/34 (29)	5/15 (33)	5/19 (26)	.656
Left anterior descending artery	9/34 (27)	4/15 (27)	5/19 (26)	.982
Circumflex artery	3/34 (9)	0/15 (0)	3/19 (16)	.107
Right coronary artery	12/34 (35)	6/15 (40)	6/19 (32)	.609
Cardiac magnetic resonance imaging features	19 (51)	9 (53)	10 (50)	.630
Time between hospital admission and cardiac magnetic resonance imaging, d	13 [5-19]	10 [5-19]	14 [6-30]	.353
Late gadolinium enhancement (n = 9)	9/19 (47)	4/9 (44)	5/9 (56)	.653
Late gadolinium enhancement pattern				.956
Subendocardial pattern	5/9 (56)	2/4 (50)	3/5 (60)	
Subepicardial pattern	2/9 (22)	1/4 (25)	1/5 (20)	
Transmural pattern	2/9 (22)	1/4 (25)	1/5 (20)	
Eosinophilic workup				
Prior eosinophil-associated disorder	15 (41)	3 (18)	12 (60)	**.009**
Main conditions underlying eosinophilia				
Antineutrophil cytoplasm antibody-negative eosinophilic granulomatosis with polyangiitis	16 (43)	3 (18)	13 (65)	**.004**
Idiopathic hypereosinophilic syndrome	12 (32)	6 (35)	6 (30)	.732
Lymphocytic-variant hypereosinophilic syndrome	1 (3)	1 (6)	0	.272
Other	8 (22)	7 (41)	1 (5)	**.008**
Extracardiac eosinophil-related organ involvement	26 (70)	9 (53)	17 (85)	**.034**
Extracardiac eosinophil-related manifestations, n	1 [0-2]	1 [0-1]	1 [1-1]	.148
Laboratory findings				
Absolute eosinophil count at admission ($\times 10^9$/L)	1.20 [0.73-1.80]	0.80 [0.54-1.80]	1.44 [0.80-2.03]	.406
Peak absolute eosinophil count during hospitalization, ($\times 10^9$/L)	1.70 [1.12-2.10]	1.60 [0.82-3.16]	1.75 [1.38-2.10]	.699
C-reactive protein at admission, mg/L	1 [0-5]	3 [0-48]	0 [0-3]	.075
High total IgE levels	8/17 (47)	3/8 (38)	5/8 (63)	.596

(continued)

TABLE I. *(Continued)*

Variable	All patients (n = 37)	Patients without vasospasm relapse (n = 17)	Patients with vasospasm relapse (n = 20)	*P*[a]
Treatments after first coronary vasospasm				
Coronary angioplasty	10/34 (29)	5/15 (33)	5/19 (26)	.656
Vasodilators	28 (76)	9 (53)	19 (95)	**.003**
Nitrates	12 (32)	3 (18)	9 (45)	.077
Calcium channel blockers	28 (76)	9 (53)	19 (95)	**.003**
Specific treatments at discharge	18 (49)	7 (41)	11 (55)	.402
Glucocorticoids	16 (43)	6 (35)	10 (50)	.368
Immunosuppressants[b]	5 (14)	1 (6)	4 (20)	.211
Pegylated IFN-α	1 (3)	1 (6)	0	.272
Imatinib	1 (3)	0	1 (5)	.350
Dupilumab biologics	2 (8)	1 (6)	1 (5)	.906
Anti-IL-5/IL-5R biologics	1 (3)	1 (6)	0	.460
Outcomes				
Follow-up, mo	30 [12-63]	25 [12-63]	31 [14-64]	.494
Persistent eosinophilia	22 (59)	3 (18)	19 (95)	**<.001**
Total recurrences during follow-up, n	3 [1-3]	—	3 [1-3]	NA
Major adverse cardiovascular event (besides coronary vasospasm)	13 (35)	6 (35)	7 (35)	.985
Third-degree atrioventricular block	5 (14)	4 (24)	1 (5)	.100
Ventricular arrhythmia	2 (6)	0	2 (10)	.180
Cardiogenic shock	8 (22)	4 (24)	4 (20)	.795
Cardiac arrest	6 (17)	2 (11)	4 (20)	.498
All causes of death	1 (3)	0	1 (5)[c]	.350
Left ventricular ejection fraction <50% at last follow-up	6 (16)	2 (12)	4 (20)	.498

NA, not available.
Results are expressed as n (%) or median [interquartile range].
Bold indicated statistical significance ($P < .05$).
[a]Patient subsets were differentiated based on the presence or not of relapse during follow-up. Qualitative variables were compared using χ^2or Fisher exact test (as appropriate), whereas Mann-Whitney test was used for continuous variables. $P \leq .05$ was considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS Institute, Carry, NC).
[b]Cyclophosphamide (n = 3) and methotrexate (n = 2).
[c]This patient died 7 y after the index hospitalization following heart-kidney transplantation for end-stage eosinophil-related heart involvement.

targeted therapies after the initial episode, relapse rates are strikingly higher than in common vasospastic angina.[4] These findings have strong practical implications and should raise awareness for physicians to check the differential counts of patients with a provisional diagnosis of Printzmetal angina. When AEC are above 0.5×10^9/L, long-term eosinophil depletion with either glucocorticoids or anti-IL-5 biologics is warranted (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

In line with the literature review of 19 cases, our findings suggest that eosinophilia-associated coronary vasospasm typically occurs in middle-aged patients who are at low cardiovascular risk but frequently display features of type 2 inflammation.[1] Strikingly, no patient with myeloid eosinophilia was reported, consistent with data on *FIP1L1:PDGFRA*-associated myeloid neoplasm with eosinophilia.[5] All coronary arteries may be involved, and both severe and diffuse spasms were observed. Although the peak AEC usually remained moderate (with only 46% of patients exceeding the HES-defining threshold of 1.5×10^9/L), the rate of major adverse cardiovascular events was high.

The pathophysiology of eosinophilia-associated coronary vasospasm remains unclear. Eosinophils are potent producers of vasospastic mediators (eg, leukotrienes C_4 and D_4[6]) and have a close bidirectional interplay with mast cells.[6] Some authors suggest that they could be embedded within the scope of allergic angina (Kounis syndrome[7]). Nevertheless, besides nonsteroidal antiinflammatory drugs, acute triggers were rare, which suggests that inflammatory processes other than IgE-related type 1 hypersensitivity could be involved. Moreover, because no patients tested positive for antineutrophil cytoplasmic antibodies or had features of vasculitis, and because most patients had low inflammatory markers (a feature that we previously showed to be associated with eosinophil-driven diseases rather than systemic vasculitis[8]), it also seems unlikely that eosinophilia-associated coronary vasospasm is related to systemic vasculitis. Nevertheless, because severe eosinophilic infiltration restricted to the adventitia and the periadventitial soft tissue was reported in an autopsic series of 11 patients with acute symptoms, eosinophilia-associated coronary vasospasm could also result from local eosinophilic coronary periarteritis.[9]

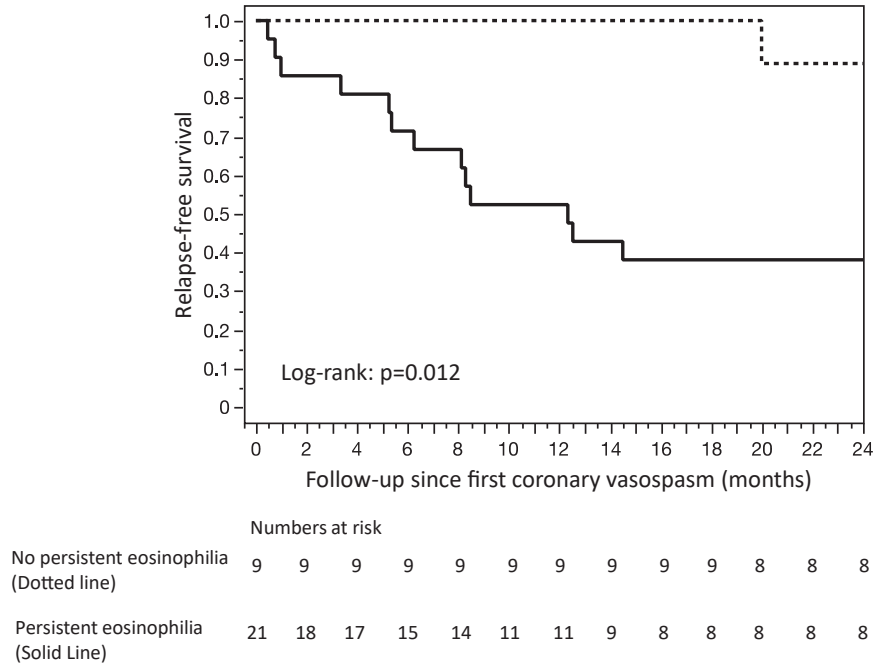

FIGURE 1. Kaplan=Meier estimates of relapse-free survival rates in patients with (*solid line*) or without (*dotted line*) persistent eosinophilia.

This study had several limitations related to its retrospective design, including missing data, no predefined treatment procedure, and loss to follow-up. Despite the close review of all individual files, we cannot rule out that patients without eosinophilia at last follow-up still had transient eosinophilia during follow-up and thus were misclassified. Moreover, this was a retrospective real-life study with no basic research and no autopsy performed. As such, the pathophysiology of eosinophilia-associated coronary vasospasm remains speculative, and there is no formal evidence that coronary artery events indeed are the consequence of type 2 inflammation within coronary arteries. Nevertheless, the current cohort is the largest ever reported in literature on the topic[1], and the fact that no patients treated with eosinophil-specific biologics relapsed suggests that eosinophils likely have a pivotal role in the disease's pathophysiology.

Eosinophilia-associated coronary vasospasm is an underrecognized, frequently relapsing, and life-threatening condition that occurs in patients with type 2 inflammation. Although treatment with vasodilators alone is inefficient, eosinophil-targeted therapies are promising.

[a]ACTION Study Group, Department of Cardiology, Foch Hospital, Suresnes, France
[b]French National Reference Center for Hypereosinophilic Syndromes, Department of Internal Medicine, Foch Hospital, Suresnes, France
[c]Department of Internal Medicine and Clinical Immunology, University of Lille, CHU de Lille, Lille, France
[d]Inserm U1286 Institute for Translational Research in Inflammation, University of Lille, CHU Lille, Lille, France
[e]Center for Medical Sciences, Department of Cellular, Computational, and Integrative Biology, University of Trento, Trento, Italy
[f]Rheumatology Unit, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari Trento, Trento, Italy
[g]Physiology Department, CHU Henri Mondor, Assistance Publique Hôpitaux de Paris, Créteil, France
[h]Intensive Cardiac Care Unit, Department of Cardiology, Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[i]Intensive Cardiac Care Unit, Cardiology Department, Bellvitge University Hospital, Bioheart, Grup de Malalties Cardiovasculars, Institut d'Investigació Biomèdica de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[j]Department of Experimental and Clinical Medicine, University of Firenze, Firenze, Italy
[k]Interdisciplinary Internal Medicine Unit, Behçet Centre and Lupus Clinic, AOU Careggi Hospital of Firenze, Firenze, Italy
[l]Internal Medicine Department, Centre National de Référence des Cytopénies Autoimmunes de l'Adulte, Hôpital Henri Mondor, Fédération Hospitalo-Universitaire Innovative Therapy for Immune Disorders, Assistance Publique Hôpitaux de Paris, Université Paris Est Créteil, Créteil, France
[m]Department of Internal Medicine and Therapeutics, Università di Pavia, Pavia, Italy
[n]Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[o]Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, Monash University, Clayton, Victoria, Australia
[p]Medical Intensive Care Unit, Hôpitaux Universitaires Henri Mondor, Assistance Publique Hôpitaux de Paris, Créteil, France
[q]Department of Pulmonology, Antony Private Hospital, Antony, France
[r]Internal Medicine, Clinique Rhéna, Strasbourg, France
[s]Department of Cardiology, Centre Hospitalier de Versailles, André Mignot Hospital, Le Chesnay-Rocquencourt, France
[t]Internal Medicine, Vesoul Hospital, Vesoul, France
[u]CHU Lille, Service de Cardiologie, Lille, France
[v]Inserm U1167, Institut Pasteur de Lille, Lille, France
[w]Department of Clinical Immunology and Internal Medicine, National Reference Center for Systemic Autoimmune Diseases (CNR RESO), Tertiary Center for Primary Immunodeficiencies, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
[x]Internal Medicine Department, Hôpital de Larchet, University Hospital of Nice, Côte d'Azur University, Nice, France
[y]Clinique des Cèdres, Château Alliez, Cornebarrieu, France
[z]Department of Intensive Care Medicine, APHP, Sorbonne Université, Pitié Salpétrière, Paris, France
[aa]Department of Cardiology, Universitary Hospital of Angers, Angers, France

[ab]Rheumatology and Clinical Immunology Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili and University of Brescia, Brescia, Italy
[ac]Department of Cardiology, University of Sorbonne−Paris Cité, APHP, Cochin Hospital, Paris, France
[ad]Department of Internal Medicine, Hôpital Cochin, APHP, Paris, France
[ae]Internal Medicine, Gabriel Montpied Hospital, Clermond-Ferrand, France
[af]Department of Cardiology, Gabriel Montpied Hospital, Clermond-Ferrand, France
[ag]Department of Cardiology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari Trento, Trento, Italy
[ah]Department of Internal Medicine, University of Paris Saclay, APHP, CHU Ambroise Paré, Boulogne-Billancourt, France
[ai]Department of Epidemiology and Public Health, Foch Hospital, Suresnes, France
[*]These authors contributed equally to this work.

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Corresponding author: Matthieu Groh, MD, MSc, Department of Internal Medicine, Foch Hospital, 40 Rue Worth, 92150 Suresnes, France. E-mail: m.groh@hopital-foch.com.

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REFERENCES

1. Wong CW, Luis S, Zeng I, Stewart RAH. Eosinophilia and coronary artery vasospasm. Heart Lung Circ 2008;17:488-96.
2. Groh M, Pineton de Chambrun M, Georges JL, Panel K, Lefèvre G, Kahn JE, et al. Recurrent cardiac arrest due to eosinophilia-related coronary vasospasm successfully treated by benralizumab. J Allergy Clin Immunol Pract 2021;9:3497-9.e1.
3. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017;38:2565-8.
4. Cho SW, Park TK, Gwag HB, Lim AY, Oh MS, Lee DH, et al. Clinical outcomes of vasospastic angina patients presenting with acute coronary syndrome. J Am Heart Assoc 2016;5:e004336.
5. Rohmer J, Couteau-Chardon A, Trichereau J, Panel K, Gesquiere C, Ben Abdelali R, et al. Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: data from 151 patients. Am J Hematol 2020;95:1314-23.
6. Galdiero MR, Varricchi G, Seaf M, Marone G, Levi-Schaffer F, Marone G. Bidirectional mast cell-eosinophil interactions in inflammatory disorders and cancer. Front Med 2017;4:103.
7. Kounis NG, Mazarakis A, Tsigkas G. Eosinophilic coronary periarteritis presenting with vasospastic angina and sudden death: a new cause and manifestation of Kounis syndrome? Virchows Arch Int J Pathol 2013;462:687-8.
8. Leurs A, Chenivesse C, Lopez B, Gibier JB, Clément G, Groh M, et al. C-Reactive protein as a diagnostic tool in differential diagnosis of hypereosinophilic syndrome and antineutrophil cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract 2019;7:1347-1351.e3.
9. Kajihara H, Tachiyama Y, Hirose T, Takada A, Saito K, Murai T, et al. Eosinophilic coronary periarteritis (vasospastic angina and sudden death), a new type of coronary arteritis: report of seven autopsy cases and a review of the literature. Virchows Arch Int J Pathol 2013;462:239-48.

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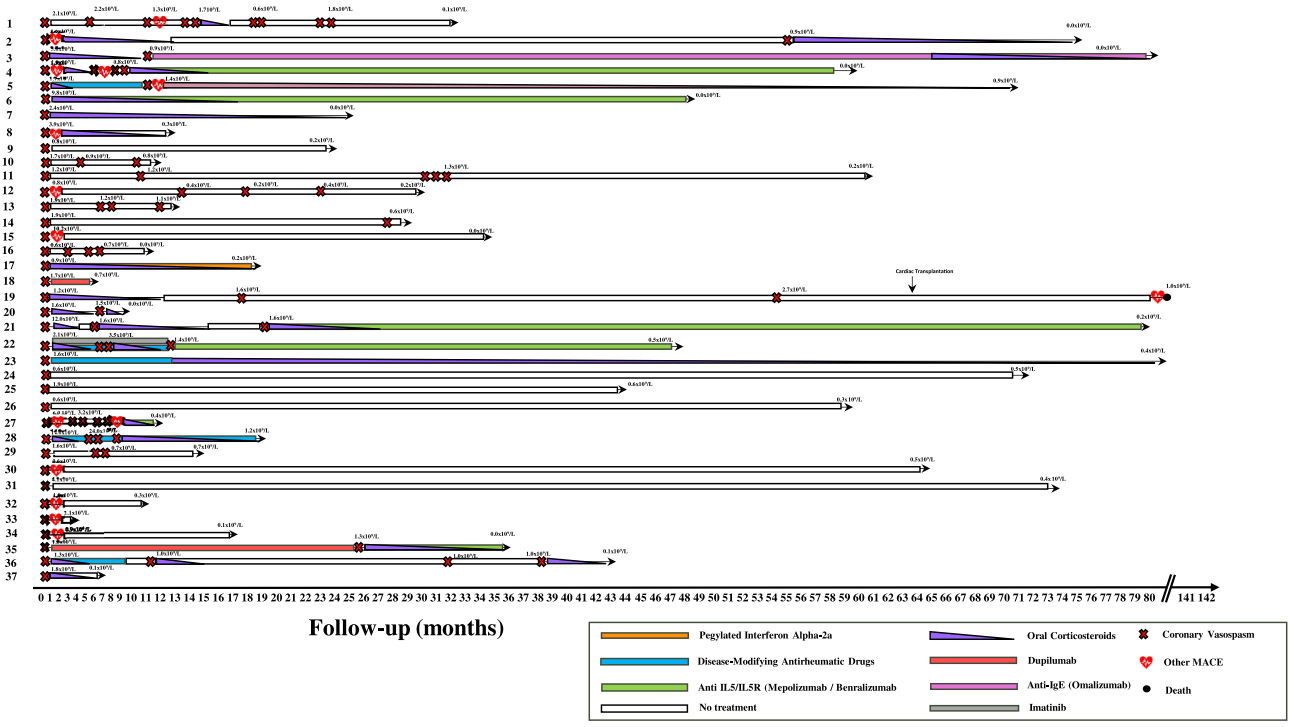

FIGURE E1. Treatment regimens and outcomes of all 37 patients with eosinophilia-associated coronary vasospasm. *MACE*, major adverse cardiovascular event.

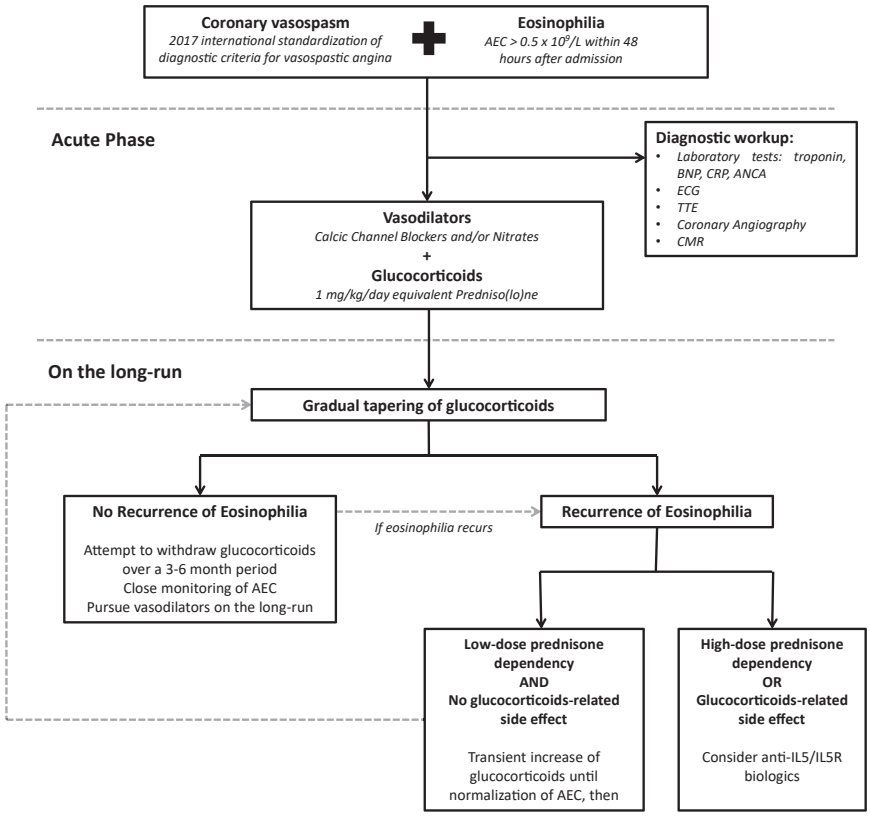

FIGURE E2. Suggested therapeutic algorithm for management of eosinophilia-associated coronary vasospasm. *AEC*, absolute eosinophil count; *ANCA*, antineutrophil cytoplasmic antibodies; *BNP*, brain natriuretic peptide; *CMR*, cardiac magnetic resonance imaging; *CRP*, C-reactive protein; *ECG*, electrocardiogram; *TTE*, transthoracic echocardiography.

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EDITED BY
Chris Wincup,
King's College Hospital NHS Foundation Trust, United Kingdom

REVIEWED BY
Shinji Izuka,
The University of Tokyo, Japan
Mehdi Jafarpour,
Tabriz University of Medical Sciences, Iran
Angelo Valerio Marzano,
University of Milan, Italy

*CORRESPONDENCE
Matthieu Groh
m.groh@hopital-foch.com

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Ophthalmic vascular manifestations in eosinophil-associated diseases: a comprehensive analysis of 57 patients from the CEREO and EESG networks and a literature review

Elisa Chapuis[1,2], Elodie Bousquet[3], Jean-François Viallard[1,4], Benjamin Terrier[5], Zahir Amoura[6], Veronica Batani[7], Antoine Brézin[8], Patrice Cacoub[9], Marco Caminati[10], Thibaud Chazal[11], Cloé Comarmond[12], Isabelle Durieu[13], Mikael Ebbo[1,14], Maximilien Grall[15], Emmanuel Ledoult[1,16], Laura Losappio[17], Irene Mattioli[18], Arsène Mékinian[19], Roberto Padoan[20], Francesca Regola[21], Jan Schroeder[18], Lior Seluk[22], Ludovic Trefond[1,23], Michael E. Wechsler[22], Guillaume Lefevre[1,24], Jean-Emmanuel Kahn[1,25], Pascal Sève[26] and Matthieu Groh[1,27]* for the French Referral Center for Hypereosinophilic Syndromes (CEREO) and European Eosinophilic Granulomatosis with Polyangiitis Study Group (EESG)

[1]National Reference Center for Hypereosinophilic Syndromes, CEREO, Suresnes, France, [2]Department of Internal Medicine, Bichat Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [3]Department of Ophthalmology, Lariboisière Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [4]Department of Internal Medicine, Bordeaux University Hospital, Bordeaux, France, [5]Department of Internal Medicine, National Referral Center for Systemic and Autoimmune Diseases, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [6]Department of Internal Medicine, Autoimmune and systemic diseases, La Pitié Salpetrière Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [7]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy, [8]Department of Ophthalmology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [9]Department of Internal Medicine and Clinical Immunology, La Pitié Salpetrière Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [10]Asthma Center and Allergy Unit, Center for Hyper-Eosinophilic Dysimmune Conditions, Department of Medicine, University of Verona, Verona, Italy, [11]Department of Internal Medicine, Hospital Fondation Adolphe de Rothschild, Paris, France, [12]Department of Internal Medicine, Competence Center for Rare Autoimmune and Inflammatory Diseases, Lariboisière Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [13]Department of Internal Medicine, Centre Hospitalier Universitaire Lyon Sud, Pierre-Bénite, France, [14]Internal Medicine Department, Hopital La Timone, APHM, Aix Marseille University, Marseille, France, [15]Department of Internal Medicine, CHU Rouen, Rouen, France, [16]Department of Internal Medicine and Clinical Immunology, CHU Lille, Lille, France, [17]Department of Clinical Immunology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [18]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [19]Department of Internal Medicine, St Antoine Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France, [20]Unit of Rheumatology, Department of Medicine DIMED, University of Padua, Padua, Italy, [21]Rheumatology and Clinical Immunology Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili and University of Brescia, Brescia, Italy, [22]Department of Medicine, National Jewish Health, Denver, CO, United States, [23]Department of Internal Medicine, Clermont-Ferrand University Hospital, Clermont-Ferrand, France, [24]Inserm, U1286 - INFINITE - Institute for Translational Research in

Inflammation, University of Lille, CHU Lille, Lille, France, [25]Department of Internal Medicine, Ambroise Pare Hospital, Assistance Publique-Hôpitaux de Paris, Boulogne, France, [26]Department of Internal Medicine, Lyon University Hospital, Lyon, France, [27]Department of Internal Medicine, Foch Hospital, Suresnes, France

Introduction: Eosinophils have widespread procoagulant effects. In daily practice, eosinophil-related cardiovascular toxicity consists of endomyocardial damage, eosinophilic vasculitis and arterial or venous thrombosis. Here we aim to report on the clinical features and treatment outcomes of patients with unexplained ophthalmic vascular manifestations and eosinophilia.

Methods: We conducted a retrospective, multicenter, observational study and a literature review of patients with eosinophilia ($\geq$0.5 x10^9/L) and concomitant ophthalmic vascular manifestations independent of the underlying eosinophilic disease but with no alternative cause for ophthalmic manifestations.

Results: Fifty-seven patients were included (20 from the observational study and 37 from the literature review). Ophthalmic vascular features were the initial manifestation of eosinophil-related disease in 34 (59%) patients and consisted of 29 central retinal artery occlusions, six branch retinal artery occlusions, five central retinal vein occlusions, two branch retinal vein occlusions, seven retinal vasculitides, two retinal vasospasms, 12 Purtscher's retinopathies, 13 anterior ischemic optic neuropathies and two posterior ischemic optic neuropathies. The median [IQR] absolute eosinophil count at onset of ophthalmic vascular manifestations was 3.5 [1.7-7.8] x10^9/L. Underlying eosinophil-related diseases included eosinophilic granulomatosis with polyangiitis (n=32), clonal hypereosinophilic syndrome (HES) (n=1), idiopathic HES (n=13), lymphocytic HES (n=2), adverse drug reactions (n=3), parasitosis (n=2), polyarteritis nodosa (n=1), IgG4-related disease (n=1), eosinophilic fasciitis (n=1) and primary sclerosing cholangitis (n=1). Other extra-ophthalmologic arterial or venous thromboses related to eosinophilia were reported in four (7%) and nine (16%) patients, respectively. Visual prognosis was poor: only eight (10%) patients achieved full recovery of ophthalmologic symptoms. After a median follow-up of 10.5 [1-18] months, one patient (3%) had a recurrence of an ophthalmic vascular manifestation, and three patients (10%) had a recurrence of other vascular symptoms (deep vein thrombosis in two and pulmonary embolism in one patient). At the time of recurrence, absolute eosinophil counts were above 0.5 x10^9/L in all cases (n=4).

Discussion: This study broadens the spectrum of vascular manifestations associated with hypereosinophilia by adding ophthalmic vascular manifestations. In patients with ophthalmological vascular manifestations and hypereosinophilia, aggressive treatment of the underlying pathology (and normalization of blood count) should be implemented.

KEYWORDS

eosinophilia, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, retinal artery occlusion, retinal vein occlusion, retinal vasculitis, optic neuropathy

Introduction

Blood and/or tissue eosinophilia is a hallmark feature of multiple allergic, infectious, inflammatory, and neoplastic disorders (1). Eosinophils have widespread effects. These include the production of procoagulant phospholipids and the production of tissue factor and activated factor XII, both of which promote the genesis of thrombin (2–4). Eosinophils also release major basic protein (MBP, which contributes to platelet activation) (5, 6), eosinophilic cationic protein, eosinophil peroxidase and platelet activation factor, all of which foster thrombus formation (7, 8). According to the latest International Cooperative Working Group on Eosinophil Disorders (ICOG-Eo), both venous and/or arterial thromboses occurring in patients with absolute eosinophil counts (AEC) > 1.5 x10^9/L are Hypereosinophilic Syndrome (HES)-defining features (9).

In daily practice, cardiovascular manifestations related to the toxicity of eosinophils mainly consist of eosinophilic myocarditis, endomyocardial fibrosis, endocardial thrombi (with potential systemic emboli) (10), venous thromboembolism (11), and eosinophilic vasculitis in patients with idiopathic HES (12, 13) Eosinophilia can also be associated with organ and/or life-threatening manifestations *e.g.*, thromboangiitis obliterans-like disease (14, 15), coronary vasospasm (16) or ischemic strokes of border zone distribution (17), all of which can have poor outcomes (18). To date, ophthalmic vascular manifestations (*e.g.* central retinal artery occlusion (CRAO), Purtscher's retinopathy, central retinal vein occlusion (CRVO) or ischemic optic neuropathy (ION)) have seldom been reported in the setting of eosinophil-associated disorders, consisting mostly of case reports or small case series (19–22). Hence, the management of such patients is not standardized.

Here, we aim to report on the clinical picture and treatment outcomes of patients with ophthalmic vascular manifestations and eosinophilia, and ultimately to provide a data-driven practical therapeutic algorithm.

Materials and methods

Study design and inclusion criteria

We conducted a retrospective, multicenter, observational study. Centers involved in the French National Reference Center for HES (CEREO) and in the European Eosinophilic Granulomatosis with Polyangiitis study group as well as 1 US center of EGPA expertise (National Jewish Health, NJH) were queried to identify patients with: (i) at least one episode of ophthalmic vascular manifestation (CRAO, branch retinal artery occlusion (BRAO), CRVO, branch retinal vein occlusion (BRVO), Purtscher's retinopathy, retinal vasculitis or ION); (ii) concomitant absolute eosinophilia count (AEC) ≥ 0.5 x10^9/L when the ophthalmic vascular manifestation occurred. Exclusion criteria were the presence of any condition, comorbidity or concomitant treatment leading to thrombophilia (either constitutional or acquired), cardiac embolism, rhythmic heart disease, tight carotid stenosis (NASCET ≥70%) homolateral to the retinal involvement or other causes of Purtscher's retinopathy (*e.g.* acute pancreatitis, head trauma or thrombotic microangiopathy), ION (*e.g.* giant cell arteritis) as well as the presence of anti-myeloperoxydase (MPO) anti-neutrophil cytoplasmic autoantibodies. A comprehensive list of exclusion criteria is provided in the Supplementary Appendix.

Literature review

The PUBMED database was searched for English-language publications released up to April 2023, using the following combination of MeSH terms: (i) 'hypereosinophilic syndrome' (or any term referring to a condition embedded within the spectrum of clonal, reactive (including lymphocytic HES, drug-induced or paraneoplastic eosinophilia) and idiopathic HES (including single-organ and systemic eosinophil-associated diseases)); (ii) and a MeSH term referring to an ophthalmic vascular manifestation (*e.g.*, retinal artery occlusion, retinal vein occlusion, retinal vasculitis, retinal diseases, optic neuropathy). Reference lists from selected publications were screened for additional relevant studies.

Baseline measurements

All cases were reviewed by the investigators (EC, MG) considering the entire follow-up. Using a standardized de-identified case report form, demographic (including cardiovascular and venous thromboembolism risk factors), clinical, laboratory and imaging findings at the time of the ophthalmic vascular manifestation as well as during follow-up were collected. For each patient, the underlying process underpinning blood hypereosinophilia was assessed according to the International COoperative study Group on Eosinophil disorders (ICOG-Eo) terminology (9) and thus considered as either clonal (*i.e.* neoplastic, including *FIP1L1::PDGFRA* myeloid neoplasm with eosinophilia), reactive (including all conditions that lead to the production of type 2 inflammation-related cytokines and thereby to non-clonal HE), overlapping (when embodied within the spectrum of autoimmune diseases, *e.g.* MPO ANCA-negative EGPA (23), IgG4-related disease (24), or eosinophilic fasciitis (25)), or idiopathic.

Outcomes

For patients with ≥ 3 months of follow-up, and after exclusion of patients with single-flare eosinophilia (parasitosis and drug-induced eosinophilia), studied outcomes included visual acuity at last follow-up, the recurrence of either ophthalmic or extra-ophthalmologic vascular events, the occurrence of ophthalmic complications (*e.g.* retinal neovascularization, intravitreal hemorrhage or neovascular glaucoma), and death. Full ophthalmic recovery was defined as the resolution of ophthalmologic symptoms (full correction of visual acuity, visual field normalization, no recurrence of transient monocular blindness). Partial recovery was defined as partial improvement in visual acuity and/or visual field.

Statistical analysis

Patient characteristics are reported as median [interquartile] ([IQR]) and frequency (percentage) for continuous and categorical variables, respectively. Visual acuity was converted into the log of the minimum angle of resolution (logMAR). Patient subsets were differentiated based on the subtype of vascular manifestation (arterial involvement *vs.* venous thrombosis *vs.* Purtscher's retinopathy). Visual outcomes were compared using the Chi-squared test and continuous variables were compared using the Kruskal Wallis test.

Ethical and regulatory considerations

All methods were carried out in accordance with relevant guidelines and regulations (*i.e.* the Good Clinical Practice protocol, the Declaration of Helsinki principles and the MR004 French legislation regarding observational retrospective studies) and this study was approved by the independent ethics committee of Foch Hospital (IRB00012437, approval number 23-03-04).

Results

Patient identification and baseline characteristics

One hundred and twenty-three patients were screened through the CEREO, EESG and NJH databases, and 55 case reports (corresponding to 56 patients) treated for eosinophilia and concomitant ophthalmic vascular manifestations were identified through the literature review. Overall, 57 patients fulfilled inclusion criteria (20 from the observational study and 37 from the literature review, Figure 1). Their main characteristics are reported in Table 1. Thirty-two (56%) were male and their median age at ophthalmic manifestation onset was 54 [44-65] years. Thirty-six (58%) had at least one cardiovascular risk factor, three (5%) had a prior history of cardiovascular disease and four (7%) had a prior history of venous thromboembolism. Among the 55 patients with available data, only one (2%) developed ophthalmic vascular involvement despite ongoing treatment with both antiplatelets and anticoagulants.

Ophthalmologic symptoms were the initial eosinophil-related organ involvement in 34 (59%) patients, while 23 (41%) had already been diagnosed with a prior eosinophil-associated disease, including 17 (30%) who were currently treated with systemic corticosteroids at the time of ophthalmic vascular involvement and four (7%) who had prior eosinophil-related venous thromboembolism. Among the seven patients with available data, the median delay between eosinophil-related first manifestation and ophthalmic symptoms was 36 [15-96] months. The median AEC at onset of ophthalmic vascular manifestation was 3.5 [1.7-6.8] $x10^9$/L. Among the 40 patients (70%) with available data, the median peak AEC during follow-up was 4.6 [2-8.9] $x10^9$/L, including 37 (92%) patients with hypereosinophilia > 1.5 $x10^9$/L (*i.e.* the HES-defining threshold). Among the 48 patients with extra-ophthalmologic eosinophil-related organ involvement, the median number of organs involved was two [1-3], consisting mostly of peripheral nervous system (n=23), skin (n=28), lung (n=16), ENT (n=17) and musculoskeletal (n=12) manifestations. Of note, four (7%) patients reported features of arterial thrombosis (ischemic stroke n=2, acute coronary syndrome and gastrointestinal tract ischemia, a single patient each), nine (16%) of venous thromboembolism (pulmonary embolism n=4, lower limb deep venous thrombosis n=3, inferior vena cava thrombosis, pulmonary vein thrombosis, a single patient each), and four (7%) had eosinophilic myocarditis. Among the 13 thrombotic manifestations, seven occurred concomitantly with

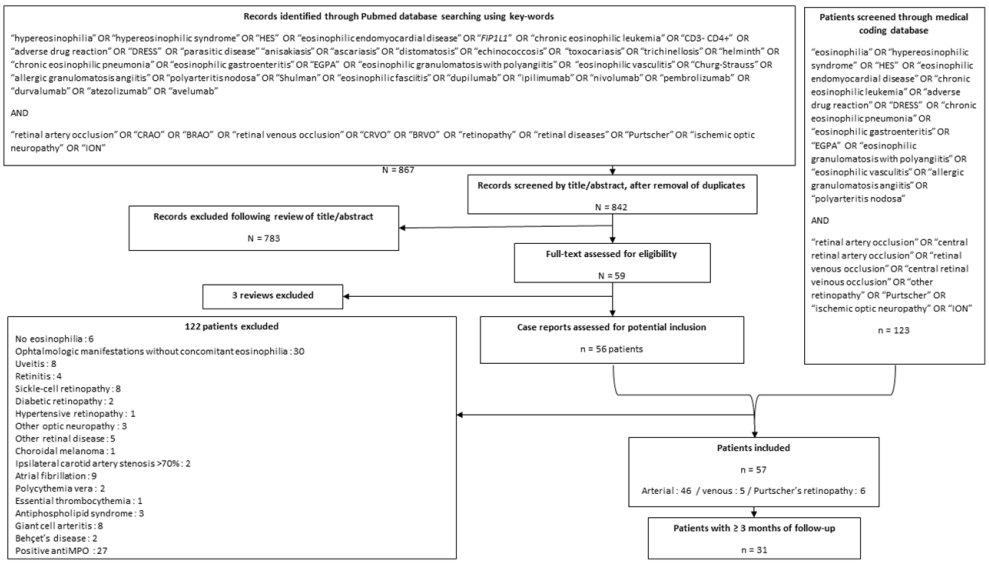

FIGURE 1
Flow-chart showing the search strategy and inclusion/exclusion criteria for the study population.

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TABLE 1 Baseline demographic, clinical, biological and treatment features of patients with ophtalmic vascular manifestations and eosinophilia.

	All patients (n=57, eyes 78)	Arterial involvement (n=46, eyes 59)	Venous involvement (n=5, eyes 7)	Purtscher's retinopathy (n=6, eyes 12)
Demographics				
Sex, female	25 (44)	18 (39)	3 (60)	4 (67)
Age, years	54 [44-65]	56 [46-66]	53 [45-56]	39 [32-45]
Cardiovascular risk factors				
Age > 50years (man) or > 60years (woman)	30 (53)	27 (59)	2 (40)	1 (17)
Active smoker	3/38 (8)	3/29 (10)	0 (0)	0 (0)
Hypertension	13/38 (34)	9/29 (31)	2 (40)	2 (33)
Diabetes	6/38 (16)	3/29 (10)	2 (40)	1 (17)
Dyslipidemia	1/38 (3)	1/39 (3)	0	0
Number of cardiovascular risk factors	1 [0-1]	1 [0-1]	1 [1-1]	0 [0-0]
Prior history of cardiovascular disease	3 (5)	3 (7)	0	0
Prior history of venous thromboembolic disease	4 (7)	2 (4)	1 (20)	1 (20)
Ophthalmological findings				
Bilateral involvement	21 (37)	13 (28)	2 (40)	6 (100)
Ophthalmological symptoms				
Visual acuity loss	71 (91)	52 (88)	7 (86)	12 (100)
Visual field abnormalities	9 (12)	7 (12)	0 (0)	2 (20)
Transient monocular blindness	13 (17)	12 (20)	1 (14)	0
Visual acuity (logmar)	1.7 [0.5-2.3]	2 [0.8-2.3]	0.45 [01-0.88]	1.7 [0.5-1.7]
Fundus abnormalities	64/64 (100)	47/47 (100)	5/5 (100)	12/12 (100)
Fluorescein angiography abnormalities	37/39 (95)	27/29 (93)	2/2 (100)	8/8 (100)
Optical Coherence Tomography abnormalities	14/18 (78)	5/9 (56)	3/3 (100)	616 (100)
Visual field defects	14/17 (82)	12/15 (80)	0/0	2/2 (100)
Ophtalmological diagnoses				
CRAO	29	29	–	–
BRAO	6	6	–	–
AION	13	13	–	–
PION	2	2	–	–
Vasculitis	7	7	–	–
Retinal vasospasm	2	2	–	–
Purtscher 's retinopathy	10	–	–	12
CRVO	5	–	5	–
BRVO	2	–	2	–
Eosinophilic workup				
Prior eosinophil-associated disorder	23 (41)	17 (37)	4 (80)	2 (33)
Main conditions underlying eosinophilia				
Clonal HES	1 (2)	1 (2)	0	0
Idiopathic HES	13 (23)	7 (15)	2 (40)	4 (67)

(Continued)

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TABLE 1 Continued

	All patients (n=57, eyes 78)	Arterial involvement (n=46, eyes 59)	Venous involvement (n=5, eyes 7)	Purtscher's retinopathy (n=6, eyes 12)
Lymphocytic HES	2 (4)	2 (4)	0	0
EGPA	32 (57)	30 (65)	2 (40)	0
Polyarteritis nodosa	1 (2)	1 (2)	0	0
Parasitosis	2 (4)	2 (4)	0	0
Adverse drug reaction	3 (5)	1 (2)	0	2 (33)
Others	3 (5)	2 (4)	1 (20)	0
Extra-ophthalmological eosinophil- related organ involvement	48 (86)	39 (88)	4 (80)	5 (100)
n of other organs involved	2 [1-3]	2 [1-3]	2 [2-3]	3 [3-4]
Arterial thrombosis	4 (7)	4 (9)	0	0
Venous thrombosis	9 (16)	6 (13)	2 (40)	1 (20)
Heart	4 (7)	4 (9)	0	0
Lung	16 (29)	11 (24)	3 (60)	2 (40)
Skin	28 (50)	22 (48)	2 (40)	4 (80)
Gastrointestinal tract	2 (4)	2 (4)	0	0
ENT	17 (30)	16 (35)	1 (20)	0
Central nervous system	4 (7)	2 (4)	1 (20)	1 (20)
Peripheral nervous system	23 (41)	22 (48)	1 (20)	0
Kidney	3 (5)	1 (2)	1 (20)	1 (20)
Musculoskeletal	12 (21)	8 (17)	2 (40)	2 (40)
Effusion of serous cavities	2 (4)	1 (2)	0	1 (20)
Liver and biliary tract	4 (7)	2 (4)	1 (20)	1 (20)
Laboratory findings				
AEC at admission for ophthalmologic event, x 10^9/L	3.5 [1.7-6.8]	3 [1.6-4.7]	3 [1.8-5.9]	5 [5-30]
Maximum AEC , x 10^9/L	4.6 [2-8.9]	4.2 [2-8.1]	3 [1.8-5.9]	5 [5-30]
ANCA positive	8/36 (22)	7/25 (28)	1/3 (33)	0
CRP > 40mg/L	7/32 (22)	7/28 (25)	0/3 (0)	1/1 (100)
Elevated tryptase	0/11 (0)	0/9	0/1	0/1
Elevated IgE	9/12 (75)	8/10 (80)	1/1 (100)	0/1 (0)
Treatments				
After the ophthalmic event				
Glucocorticoids	45 (79)	39 (85)	0	6 (100)
Immunosuppressants	12 (21)	12 (26)	0	0
Intravenous immunoglobulins	1 (2)	1 (2)	0	0
Plasma exchanges	2 (4)	2 (4)	0	0
Antiparasitic therapy	1 (2)	1 (2)	0	0
Fibrinolysis	5 (9)	5 (11)	0	0
Ocular hypotensive therapy	4 (7)	4 (9)	0	0
During the entire follow-up				

(Continued)

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TABLE 1 Continued

	All patients (n=57, eyes 78)	Arterial involvement (n=46, eyes 59)	Venous involvement (n=5, eyes 7)	Purtscher's retinopathy (n=6, eyes 12)
Glucocorticoids	48 (84)	41 (89)	1 (20)	6 (100)
Immunosuppressants	20 (36)	19 (41)	1 (20)	0
Anti -IL5/IL5R	7 (13)	6 (13)	1 (20)	0
Imatinib	2 (4)	2 (4)	0	0
Hydroxyurea	2 (4)	2 (4)	0	0
Infiximab	1 (2)	1 (2)	0	0
Rituximab	3 (5)	2 (4)	1 (20)	0
Plasma exchanges	2 (4)	2 (4)	0	0
Antiparasitic therapy	3 (5)	3 (7)	0	0
Intravenous immunoglobulins	1 (2)	1 (2)	0	0
Antiplatelets	21 (38)	20 (43)	1 (20)	0
Anticoagulants	9 (16)	7 (15)	2 (40)	0

Data are reported as no. (%) or median [IQR], unless otherwise specified.
AEC, absolute eosinophil count; AION, anterior ischemic optic neuropathy; BRAO, branch retinal artery occlusion; BRVO, branch retinal vein occlusion; CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear nose and throat; HES, hypereosinophilic syndrome; PION, posterior ischemic optic neuropathy.

ophthalmic vascular manifestations. Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) was the leading cause driving eosinophilia (n=32, 57%). Other associated conditions included *STAT5A*-associated chronic eosinophilic leukemia (n=1, 2%), lymphocytic (n=2, 4%), idiopathic (n=13, 23%), reactive (n=5, 7% including three drug adverse reactions and two parasitosis) HES as well as overlapping diseases (n=4, 7%, consisting of polyarteritis nodosa, IgG4-related disease, sclerosing cholangitis and eosinophilic fasciitis, a single patient each).

Ophthalmological findings

Ocular involvement was bilateral in 21 patients (37%), and in the remaining patients there was no predominant eye involved. Ophthalmic vascular manifestations included CRAO (n= 24 patients, 29 eyes), BRAO (n= 5 patients, 6 eyes), CRVO (n= 3 patients, 5 eyes), BRVO (n= 2 patients, 2 eyes), retinal vasculitis (n= 5 patients, 7 eyes), retinal vasospasm evidenced upon fluorescein angiography (one patient with bilateral involvement), Purtscher's retinopathy (n=6 patients, 12 eyes), anterior ischemic optic neuropathy (n= 10 patients, 13 eyes) and posterior ischemic optic neuropathy (n=2 patients with unilateral involvement). Ocular symptoms (present in all patients but one) consisted of vision loss (53 patients, 71 eyes), transient monocular blindness (11 patients, 13 eyes) and visual field abnormalities (7 patients, 9 eyes). The median visual acuity at diagnosis was 1.7 [0.5-2.3] logmar. In all eyes with available data (n=64 eyes), fundus examination was always abnormal (fundus data of the 2 patients with posterior ischemic optic neuropathy were not available). Among the 39 fluorescein angiographies that were performed, imaging findings were abnormal and concordant with the clinical diagnoses suspected upon fundus examination in 37 (95%) cases. Figure 2 illustrates the retinal imaging finding of a patient with CRAO in the left eye. Among the 28 patients with imaging of supra-aortic arteries, 8 (29%) had evidence of mild (NASCET < 70%) ipsilateral carotid artery atheroma. Of note, among the 22 patients with available concomitant brain imaging (cerebral MRI or injected TDM), cerebral ischemic events were reported in two (5%) cases.

Treatment regimens

At the acute phase, forty-five (79%) patients received systemic corticosteroids (oral corticosteroids, n=23; intravenous corticosteroids n=22; starting doses ranging from 10mg to 1mg/kg/day of prednisone or equivalent before gradual tapering). Twelve (21%) patients received immunosuppressants, including cyclophosphamide (n=8), azathioprine (n=3) and methotrexate (n=1). Fibrinolytic agents and ocular hypotensive therapy were prescribed in five (9%) and four (7%) patients, respectively, while nine (16%) and 21 (38%) patients received long-term anticoagulants or antiplatelets, respectively. Other treatments consisted of antiparasitic drugs (n=1), plasma exchanges (n=2) and intravenous immunoglobulins (n=1).

During follow-up, other treatments included imatinib (n=2), hydroxyurea (n=2) and infliximab (n=1).

Outcomes

Full details of patients' outcomes are provided in Table 2. Among the 50 (88%) patients with available follow-up data (including 30 with

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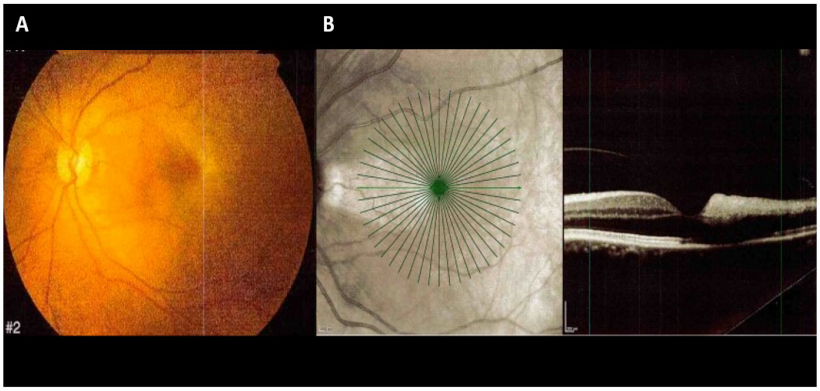

FIGURE 2
Color fundus photography and spectral domain optical coherence tomography (SD-OCT) of a 43-year-old woman with eosinophilia and central retinal artery occlusion (CRAO) in the left eye. **(A)** Color fundus photography illustrates a retinal whitening of the posterior pole indicative of a CRAO with preservation of the cilioretinal artery. **(B)** SD-OCT shows hyperreflectivity in the temporal middle and inner retinal layer hyperreflectivity consistent with CRAO and cilioretinal artery sparing.

more than three months of follow-up), the median follow-up after the initial ophthalmic vascular manifestation was 10.5 [1-18] months. One (3%) patient had a recurrence of ophthalmic vascular manifestation (CRVO) and three (10%) patients had another vascular event (lower limb deep vein thrombosis n=2, pulmonary embolism n=1). In all cases, AEC was above 0.5 x10^9/L at time of recurrence. At last follow-up, only six patients (12%) achieved full recovery. Sixteen patients (32%) achieved partial recovery, 23 patients (46%) stabilized once under treatment, while the condition of the remaining five patients (10%) worsened despite therapy. By comparison with patients with arterial involvement, the rate of ophthalmic recovery was higher in patients with either Purtscher's retinopathy or venous involvement (recovery achieved in 8/10 eyes with Purtscher's retinopathy and in 4/5 eyes with venous involvement *vs* 18/53 eyes with arterial involvement, p=0.019). Patients with venous involvement or Purtscher's retinopathy had a better visual acuity at last follow-up than patients with arterial involvement (median logmar 0 [0-0], 1 [0-2.3] and 0.5 [0.2-0.8] for patients with venous, arterial involvement and Purtscher's retinopathy

TABLE 2 Outcomes of patients with ophthalmic vascular manifestations and eosinophilia.

	All patients (n=57, 78 eyes)	Arterial involvement (n=46, 59 eyes)	Venous involvement (n=5, 7 eyes)	Purtscher's retinopathy (n=6, 12 eyes)
Follow-up time (month)	10.5 [1-18]	11 [1-31]	8.5 [3.8-12]	6 [1-12]
Visual status at last follow-up (eyes)				
Worsening	8 (10)	8 (14)	0	0
Stability	30 (38)	27 (46)	1 (20)	2 (20)
Partial recovery	22 (28)	14 (24)	0	8 (80)
Full recovery	8 (10)	4 (7)	4 (80)	0
Visual acuity at last follow-up (logmar)	0.5 [0-2]	1 [0-2.3]	0 [0-0]	0.5 [0.2-0.8]
Ophthalmological complications	3 (10)	3 (13)	0	0
Vascular ophthalmologic recurrence	1 (3)	0	1 (33)	0
Other outcomes (n = 30 patients)				
Other vascular event	3 (10)	3 (13)	0	0
Death	4 (7)	3 (7)	0	1 (20)

Data are reported as no. (%) or median [IQR].

respectively; p= 0.038). Of note, the levels of baseline absolute eosinophil counts did not correlate with long-term visual outcomes, and there were no significant differences regarding the final visual acuities of patients who received antiplatelets vs. anticoagulants as well as in patients who received only corticosteroids vs. those who received both corticosteroids and immunosuppressants (data not shown).

Three (10%) patients developed retinal neovascularization with subsequent intravitreal hemorrhage during follow-up. During follow-up, four patients died of pulmonary infection, MRSA-induced septic shock, endomyocardial fibrosis and hepatitis (a single patient each). Both patients who died of sepsis were treated by systemic corticosteroids (in addition to methotrexate or mepolizumab, a single patient each).

Focus on patients with EGPA

Thirty-two (57%) patients fulfilled MIRRA and/or ACR criteria for EGPA (all without MPO-ANCA). In the latter patients, ophthalmic vascular manifestations consisted of CRAO (17 patients, 21 eyes), BRAO (a single patient with unilateral involvement), AION (8 patients, 11 eyes), PION (a single patient with unilateral involvement), retinal vasculitis (3 patients, 4 eyes), CRVO (a single patient with bilateral involvement) and BRVO (a single patient with unilateral involvement). It was noteworthy that no patient with EGPA had Purtscher's retinopathy. Extra-ophthalmic vascular manifestations included both eosinophilic-driven (*e.g.* eosinophilc myocarditis or central nervous system involvement, a single patient each) and vasculitic (*e.g.* mononeuritis multiplex n=18 patients and purpura, n=12 patients) manifestations. Among the 19 patients with available data, only five (26%) had mild elevation of C-reactive protein (CRP) levels (<40mg/L).

The visual prognosis of EGPA patients was poor and the median final visual acuity was 2 [0.1-2.4] logmar. Among the fourteen patients with at least three months of follow-up, only one patient recovered completely and three achieved partial recovery, whereas two patients worsened and eight had a stability of their visual acuity. Moreover, three patients (21%) had a new vascular event during follow-up (lower limb deep vein thrombosis, n=2; pulmonary embolism, n=1). None of the 32 EGPA patients died during follow-up.

Discussion

Recent advances have led to the better understanding of the mechanisms driving the pro-coagulant effects of eosinophils (26), and reported cases of arterial and venous thrombotic manifestations related to eosinophilia have increased (11, 15–17, 19). Likewise, the spectrum of eosinophilia-related cardiovascular toxicity has now broadened beyond the scope of eosinophilic cardiomyopathy (10). Some studies have recently highlighted peculiar phenotypes *e.g.*, thromboangiitis obliterans-like disease (14), eosinophilia-associated coronary vasospasm (16) or ischemic strokes of border zone distribution (17). Here, we shed further light on the diversity of eosinophil-induced vascular symptoms and report on various ophthalmic vascular manifestations occurring within the full-spectrum of eosinophil-related diseases, either as first disease manifestation or during follow-up.

Intracardiac thrombus and peripheral arterial emboli were the main features reported in the review of HES-related cardiovascular manifestations reported by Ogbogu et al (10). Likewise, in the main series of patients with HES, ophthalmic vascular manifestations have rarely been reported (19, 27, 28), and mostly consist of case reports or small case series (20–22). In their 2019 review of 189 patients with idiopathic eosinophilic vasculitis, Lefevre et al. reported on only one case of CRAO and one case of retinal vasculitis (12). Among 151 patients with *FIP1L1::PDGFRA*-related HES, only one case of CRAO was reported (19) and in another series of 26 patients with $CD3^{-}CD4^{+}$ lymphocytic HES, none presented with ophthalmic symptoms (27). Dupilumab-induced Purtscher's retinopathy with eosinophilia reported herein is in line with dupilumab-induced eosinophilic vasculitis that our group has previously reported (29). EGPA is the only eosinophil-associated disease for which ophthalmic vascular manifestations have been more extensively depicted, with predominant arterial involvement and poor visual prognosis despite treatment with corticosteroids (30, 31).

Here, we report on a wide variety of ophthalmic vascular manifestations related to eosinophil-associated disorders, that clustered into three main clinical pictures (*i.e.* arterial or venous retinal occlusions and Purtscher's retinopathy), with one in three patients having bilateral involvement. There was no clear correlation between the clinical picture and underlying eosinophil-related diseases, supporting the fact that eosinophilia, whatever its cause, can lead to ophthalmologic vascular toxicity. Nevertheless, both clonal and lymphocytic HES were rare (one and two patients respectively), and EGPA was never reported in the setting of Purtscher's retinopathy. Strikingly, other (and most often concomitant) extra-ophthalmologic vascular manifestations related to eosinophilia were reported in up to 15% of patients, including organ or life-threatening events *e.g.*, ischemic strokes, acute coronary syndrome, gastrointestinal tract ischemia, or inferior vena cava thrombosis. Although skin, lung and gastrointestinal symptoms are the most frequent manifestations of HES, the latter is a multifaceted disease and some patients have prominent vascular manifestations, including catastrophic antiphospholipid syndrome-like presentation (11). As expected (32–35), the visual prognosis was poor (with only six patients achieving full recovery and significant loss of visual acuity at last follow-up), especially in patients with ION or CRAO.

In this series, patients had few cardiovascular risk factors and no major risk factor for venous thromboembolism, suggesting that their ophthalmic manifestations indeed were the consequence of eosinophil-related toxicity. There is strong evidence substantiating the procoagulant effects of eosinophils and their direct toxicity on the vascular endothelium. First, injury-induced venous thrombosis is drastically reduced in both eosinophil-deficient and eosinophil-depleted mice (2). Moreover, eosinophils are potent producers of tissue factor (2–4), can produce procoagulant phospholipids and activate factor XII, which both stimulate the intrinsic coagulation

pathway (2). Eosinophils also release major basic protein (MBP), a cationic protein that binds to thrombomodulin and thereby impairs its anticoagulant effects (5, 6). Likewise, the discharge of cytotoxic granules and pro-inflammatory mediators increases vascular permeability and induce endothelial damage, both of which contribute to a procoagulant state (26). Eosinophil extracellular DNA traps also promote platelet activation (36, 37). Lastly, since EGPA accounted for more than half of underlying eosinophil-related diseases, it is likely that underlying vasculitis also contributes to the clinical picture. Nevertheless, patients tested positive for MPO-ANCA were excluded from the study, and only a minority of patients had histologic evidence (or strong clinical surrogates) of vasculitis. Moreover, inflammatory markers tended to be low, suggesting a direct pathogenic role of eosinophils rather than systemic vasculitis (12).

As eosinophils seem to have a prominent role in the genesis of ophthalmic vascular manifestations, prompt initiation of eosinophil-targeted treatments is advisable to curb the deleterious pathophysiological process and to prevent the advent of other manifestations related to eosinophilia-related vascular toxicity. Corticosteroids are the cornerstone of the management of most eosinophilia-associated diseases (38–40). Here, 84% of patients received corticosteroids, which are rapidly effective in most cases (91%) except in a very limited number of well-defined conditions, including drug-hypersensitivity, clonal HES, and paraneoplastic eosinophilia (18). The use of corticosteroids has also seldom been reported in Purtscher's retinopathy or CRVO, as evidence is lacking (33, 35). Although more than one third of patients received immunosuppressants, it should be emphasized that, in both HES and EGPA, there is no evidence that the adjunction of either cytotoxic drugs or anti-interleukin 5 biologics to corticosteroids is superior to corticosteroids alone at the acute phase (38, 40). Nevertheless, as mepolizumab has demonstrated clinical efficacy and substantial steroid-sparing effect in both EGPA and HES, it is likely that such treatment is beneficial on the long run in patients with high dose steroid dependency and/or steroid-related side effects (41–43).

CRAO presents a significant challenge in ophthalmology, as it often leads to irreversible retinal damage within four hours of the retinal artery occlusion. Unfortunately, there is currently no established treatment or evidence-based therapy available for non-arteritic CRAO. Numerous approaches have been attempted with the goal of dislodging emboli and enhancing retinal blood flow through various procedures, such as ocular massage, intraocular pressure reduction, isovolemic hemodilution, anticoagulation, and intraarterial fibrinolysis. These interventions have yielded poor visual outcomes (44, 45). Conversely, a strict management of cardiovascular risk factors is encouraged to manage CRVO (41), and there is no standard of treatment for Purtscher's retinopathy (35). Overall, both anticoagulants (at the acute phase) and antiplatelets (on the long run) were also frequently prescribed. As the only recurrence of ophthalmic vascular manifestation occurred in a patient with persistent eosinophilia, long-term normalization of AEC (thanks to treatment of the underlying condition) is advisable and is likely to prevent the recurrence of vascular manifestations. Of note is that in venous thromboembolism related to eosinophilia, we have previously demonstrated that anticoagulants could be safely withdrawn once complete hematological response was obtained in the long run. A suggested algorithm for the management of eosinophil-associated vascular ophthalmic involvement is provided in Figure 3.

This study has several drawbacks, including missing data and lack of standardized management within centers. Next, little follow-up data was available from the cases retrieved from the literature review, which possibly led to an underestimation of the risk of recurrence. Lastly, given the retrospective design of the study, we were unable to assess whether, besides AEC, other biological parameters (including markers of eosinophil activation and

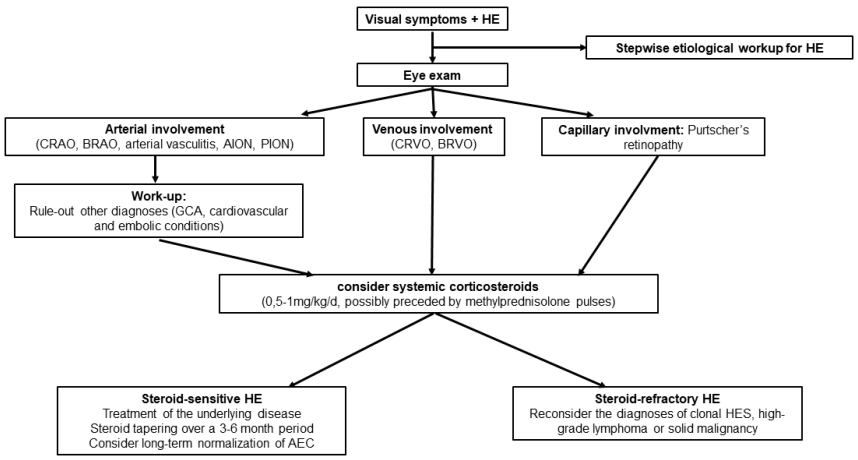

FIGURE 3
Suggested algorithm for the management of eosinophil-related ophthalmic vascular manifestations. HE, hypereosinophilia; CRAO, central retinal artery occlusion; BRAO, branch retinal artery occlusion; AION, anterior ischemic optic neuropathy; PION, posterior ischemic optic neuropathy; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; GCA, giant cell arteritis.

degranulation) could also correlate with outcomes.

Regardless of these limitations, this study – the first longitudinal analysis dedicated to ophthalmic vascular manifestations occurring during eosinophil-related diseases – emphasizes the fact that eosinophilia (whatever the underlying disease) can lead to ophthalmic vascular toxicity. It provides useful data for both ophthalmologists and physicians involved in the field of eosinophil-related disorders and suggests that, in a subset of patients with otherwise unexplained ophthalmic vascular manifestation and eosinophilia, long-term normalization of AEC is advisable to prevent the recurrence of vascular manifestations. Further large-scale studies are needed to confirm these preliminary findings, and collaborative endeavors are welcome.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by independent ethics committee of Foch Hospital (IRB00012437, approval number 23-03-04). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EC: Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Conceptualization, Methodology. EB: Writing – review & editing, Conceptualization, Data curation, Investigation. JV: Data curation, Writing – review & editing. BT: Data curation, Writing – review & editing. ZA: Data curation, Writing – review & editing. VB: Data curation, Writing – review & editing. AB: Data curation, Writing – review & editing. PC: Visualization, Writing – review & editing, Data curation. MC: Data curation, Writing – review & editing, Validation. TC: Writing – review & editing. CC: Writing – review & editing. ID: Data curation, Writing – review & editing. ME: Data curation, Writing – review & editing. MGra: Data curation, Writing – review & editing. EL: Data curation, Writing – review & editing. LL: Data curation, Writing – review & editing. IM: Data curation, Writing – review & editing. AM: Data curation, Writing – review & editing. RP: Data curation, Writing – review & editing. FR: Data curation, Writing – review & editing. JS: Data curation, Writing – review & editing. LS: Data curation, Writing – review & editing. LT: Data curation, Writing – review & editing. MW: Data curation, Writing – review & editing. GL: Data curation, Writing – review & editing. JK: Data curation, Writing – review & editing. PS: Data curation, Writing – review & editing. MGro: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1379611/full#supplementary-material

References

1. Groh M, Lefèvre G, Ackermann F, Étienne N, Kahn J-E. [Hypereosinophilic syndromes]. *Rev Prat*. (2019) 69:767–73.

2. Uderhardt S, Ackermann JA, Fillep T, Hammond VJ, Willeit J, Santer P, et al. Enzymatic lipid oxidation by eosinophils propagates coagulation, hemostasis, and thrombotic disease. *J Exp Med*. (2017) 214:2121–38. doi: 10.1084/jem.20161070

3. Cugno M, Marzano AV, Lorini M, Carbonelli V, Tedeschi A. Enhanced tissue factor expression by blood eosinophils from patients with hypereosinophilia: A possible link with thrombosis. *PloS One*. (2014) 9:e111862. doi: 10.1371/journal.pone.0111862

4. Moosbauer C, Morgenstern E, Cuvelier SL, Manukyan D, Bidzhekov K, Albrecht S, et al. Eosinophils are a major intravascular location for tissue factor storage and exposure. *Blood*. (2006) 109:995–1002. doi: 10.1182/blood-2006-02-004945

5. Mukai HY, Ninomiya H, Ohtani K, Nagasawa T, Abe T. Major basic protein binding to thrombomodulin potentially contributes to the thrombosis in patients with eosinophilia. *Br J Hematol*. (1995) 90:892–9. doi: 10.1111/j.1365-2141.1995.tb05211.x

6. Slungaard A, Vercellotti GM, Tran T, Gleich GJ, Key NS. Eosinophil cationic granule proteins impair thrombomodulin function. A potential mechanism for thromboembolism in hypereosinophilic heart disease. *J Clin Invest*. (1993) 91:1721–30. doi: 10.1172/JCI116382

7. Rohrbach M, Wheatley C, Slifman N, Gleich G. Activation of platelets by eosinophil granule proteins. *J Exp Med*. (1990) 172:1271–4. doi: 10.1084/jem.172.4.1271

8. Ojima-Uchiyama A, Masuzawa Y, Sugiura T, Waku K, Fukuda T, Makino S. Production of platelet-activating factor by human normodense and hypodense eosinophils. *Lipids*. (1991) 26:1200–3. doi: 10.1007/BF02536531

9. Valent P, Klion AD, Roufosse F, Simon D, Metzgeroth G, Leiferman KM, et al. Proposed refined diagnostic criteria and classification of eosinophil disorders and related syndromes. *Allergy*. (2023) 78:47–59. doi: 10.1111/all.15544

10. Ogbogu P, Rosing DR, Horne MK. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. (2007) 27:457–75. doi: 10.1016/j.iac.2007.07.001

11. Réau V, Vallée A, Terrier B, Plessier A, Abisror N, Ackermann F, et al. Venous thrombosis and predictors of relapse in eosinophil-related diseases. *Sci Rep*. (2021) 11:6388. doi: 10.1038/s41598-021-85852-9

12. Lefèvre G, Leurs A, Gibier J-B, Copin M-C, Staumont-Sallé D, Dezoteux F, et al. "Idiopathic eosinophilic vasculitis": another side of hypereosinophilic syndrome? A comprehensive analysis of 117 cases in asthma-free patients. *J Allergy Clin Immunol: In Pract*. (2020) 8:1329–1340.e3. doi: 10.1016/j.jaip.2019.12.011

13. Maronese CA, Derlino F, Moltrasio C, Cattaneo D, Iurlo A, Marzano AV. Neutrophilic and eosinophilic dermatoses associated with hematological Malignancy. *Front Med (Lausanne)*. (2024) 10:1324258. doi: 10.3389/fmed.2023.1324258

14. Rohmer J, Groh M, Samson M, London J, Jachiet M, Rouzaud D, et al. Distal ischemia as the initial presentation of hypereosinophilic syndrome-related arterial involvement: A case study and literature review. *Autoimmun Rev*. (2019) 18:828–30. doi: 10.1016/j.autrev.2019.06.004

15. Johnston AM, Woodcock BE. Acute aortic thrombosis despite anticoagulant therapy in idiopathic hypereosinophilic syndrome. *J R Soc Med*. (1998) 91:492–3. doi: 10.1177/014107689809100912

16. Groh M, Pineton de Chambrun M, Georges J-L, Panel K, Lefèvre G, Kahn J-E, et al. Recurrent cardiac arrest due to eosinophilia-related coronary vasospasm successfully treated by benralizumab. *J Allergy Clin Immunol: In Pract*. (2021) 9:3497–3499.e1. doi: 10.1016/j.jaip.2021.04.067

17. Tennenbaum J, Groh M, Venditti L, Campos-Gazeau F, Chalayer E, De Broucker T, et al. FIP1L1-PDGFRA-associated hypereosinophilic syndrome as a treatable cause of watershed infarction. *Stroke*. (2021) 52(10):e605–9. doi: 10.1161/STROKEAHA.121.034191

18. Gaillet A, Bay P, Péju E, Ait-Oufella H, Azoulay E, Benchabane N, et al. Epidemiology, clinical presentation, and outcomes of 620 patients with eosinophilia in the intensive care unit. *Intensive Care Med*. (2023) 49:291–301. doi: 10.1007/s00134-022-06967-9

19. Rohmer J, Couteau-Chardon A, Trichereau J, Panel K, Gesquiere C, Ben Abdelali R, et al. Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: Data from 151 patients. *Am J Hematol*. (2020) 95:1314–23. doi: 10.1002/ajh.25945

20. Chaine G, Davies J, Kohner EM, Hawarth S, Spry CJF. Ophthalmologic abnormalities in the hypereosinophilic syndrome. *Ophthalmology*. (1982) 89:1348–56. doi: 10.1016/S0161-6420(82)34625-4

21. Gupta OP, Zegere E, Maguire JI. Purtscher-like retinopathy associated with primary hypereosinophilic syndrome. *Retin cases Brief Rep*. (2009) 3:193–6. doi: 10.1097/ICB.0b013e318162b14d

22. Farcet JP, Binaghi M, Kuentz M, Merlier JF, Mayaud C, Nebout T, et al. A hypereosinophilic syndrome with retinal arteritis and tuberculosis. *Arch Internal Med*. (1982) 142:625–7. doi: 10.1001/archinte.1982.00340160205034

23. Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, et al. 2022 American College of Rheumatology/European alliance of associations for rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. *Arthritis Rheumatol*. (2022) 74:386–92. doi: 10.1002/art.41982

24. Umehara H, Okazaki K, Kawa S, Takahashi H, Goto H, Matsui S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. *Mod Rheumatol*. (2021) 31:529–33. doi: 10.1080/14397595.2020.1859710

25. Jinnin M, Yamamoto T, Asano Y, Ishikawa O, Sato S, Takehara K, et al. Diagnostic criteria, severity classification and guidelines of eosinophilic fasciitis. *J Dermatol*. (2018) 45:881–90. doi: 10.1111/1346-8138.14160

26. Khoury P, Grayson PC, Klion AD. Eosinophils in vasculitis: characteristics and roles in pathogenesis. *Nat Rev Rheumatol*. (2014) 10:474–83. doi: 10.1038/nrrheum.2014.98

27. Carpentier C, Verbanck S, Schandené L, Heimann P, Trépant A-L, Cogan E, et al. Eosinophilia associated with CD3–CD4+ T cells: characterization and outcome of a single-center cohort of 26 patients. *Front Immunol*. (2020) 11:1765. doi: 10.3389/fimmu.2020.01765

28. Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, et al. Hypereosinophilic syndromes: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol*. (2009) 124:1319–25.e3. doi: 10.1016/j.jaci.2009.09.022

29. Descamps V, Deschamps L, El Khalifa J, Groh M, Gibier J-B, Lefèvre G, et al. Eosinophilic vasculitis associated with persistent dupilumab-induced hypereosinophilia in severe asthma. *Respir Med Res*. (2021) 79:100821. doi: 10.1016/j.resmer.2021.100821

30. Takanashi T, Uchida S, Arita M, Okada M, Kashii S. Orbital inflammatory pseudotumor and ischemic vasculitis in Churg-Strauss syndrome: Report of two cases and review of the literature11The authors have no proprietary interest in any aspect of this study. *Ophthalmology*. (2001) 108:1129–33. doi: 10.1016/S0161-6420(01)00557-7

31. Akella SS, Schlachter DM, Black EH, Barmettler A. Ophthalmic eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome): A systematic review of the literature. *Ophthalmic Plast Reconstruct Surg*. (2019) 35:7. doi: 10.1097/IOP.0000000000001202

32. Madike R, Cugati S, Chen C. A review of the management of central retinal artery occlusion. *Taiwan J Ophthalmol*. (2022) 12:273–81. doi: 10.4103/2211-5056.353126

33. Blair K, Czyz CN. Central retinal vein occlusion. In: *StatPearls*. Treasure Island, Florida, United States of America: StatPearls Publishing (2023).

34. Luneau K, Newman NJ, Biousse V. Ischemic optic neuropathies. *Neurologist*. (2008) 14:341–54. doi: 10.1097/NRL.0b013e318177394b

35. Tripathy K, Patel BC. Purtscher retinopathy. In: *StatPearls*. Treasure Island, Florida, United States of America: StatPearls Publishing (2023).

36. Marx C, Novotny J, Salbeck D, Zellner KR, Nicolai L, Pekayvaz K, et al. Eosinophil-platelet interactions promote atherosclerosis and stabilize thrombosis with eosinophil extracellular traps. *Blood*. (2019) 134:1859–72. doi: 10.1182/blood.2019000518

37. Ueki S, Melo RCN, Ghiran I, Spencer LA, Dvorak AM, Weller PF. Eosinophil extracellular DNA trap cell death mediates lytic release of free secretion-competent eosinophil granules in humans. *Blood*. (2013) 121:2074–83. doi: 10.1182/blood-2012-05-432088

38. Groh M, Rohmer J, Etienne N, Abou Chahla W, Baudet A, Chan Hew Wai A, et al. French guidelines for the etiological workup of eosinophilia and the management of hypereosinophilic syndromes. *Orphanet J Rare Dis*. (2023) 18:100. doi: 10.1186/s13023-023-02696-4

39. Klion AD. How I treat hypereosinophilic syndromes. *Blood*. (2015) 126:1069–77. doi: 10.1182/blood-2014-11-551614

40. Emmi G, Bettiol A, Gelain E, Bajema IM, Berti A, Burns S, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev. *Rheumatol*. (2023) 19:378–93. doi: 10.1038/s41584-023-00958-w

41. Nicholson L, Talks SJ, Amoaku W, Talks K, Sivaprasad S. Retinal vein occlusion (RVO) guideline: executive summary. *Eye (Lond)*. (2022) 36:909–12. doi: 10.1038/s41433-022-02007-4

42. Howard RC, Welch MN, Hager AC, Zumbro DS. Purtscher-like retinopathy and primary hypereosinophilic syndrome association. *Retin cases Brief Rep*. (2012) 6:273–7. doi: 10.1097/ICB.0b013e318228e32b

43. Fong A, Ahmed S, Ramalingam S, Brown RM, Harper L, Mollan SP. Eosinophilic granulomatosis with polyangiitis presenting as unilateral acute anterior ischemic optic neuropathy. *Neuroophthalmology*. (2021) 45:109–16. doi: 10.1080/01658107.2020.1761402

44. Schumacher M, Schmidt D, Jurklies B, Gall C, Wanke I, Schmoor C, et al. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. *Ophthalmology*. (2010) 117:1367–1375.e1. doi: 10.1016/j.ophtha.2010.03.061

45. Lin JC, Song S, Ng SM, Scott IU, Greenberg PB. Interventions for acute non-arteritic central retinal artery occlusion. *Cochrane Database Syst Rev*. (2023) 1:CD001989. doi: 10.1002/14651858.CD001989.pub3

2.3 STUDIES ON ANCA-ASSOCIATED VASCULITIDES

In the following chapters, multicenter collaborative studies on ANCA-associated vasculitides will be presented. The studies included are as follows:

- Hospitalization rates and features of a large multicentric cohort of patients with ANCA-associated vasculitis

- Overlapping Forms of Eosinophilic Granulomatosis with Polyangiitis and Granulomatosis with Polyangiitis: Presentation, Management and Outcomes

- Validation of the Italian version of the ANCA-associated vasculitis patient-reported outcome (AAV-PRO) questionnaire

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Hospitalization rates and features of a large multicentric cohort of patients with ANCA-associated vasculitis

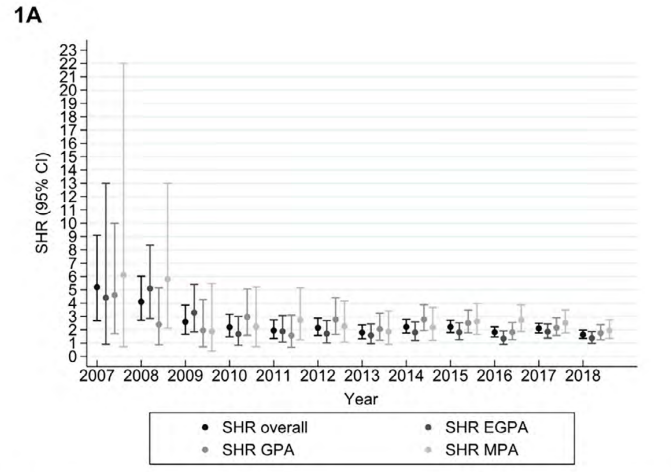
Alvise Berti[1], Pamela Mancuso[2], Silvia Sartorelli[3], Elena Treppo[4], Alessandra Bettiol[5], Roberto Padoan[6], Francesca Regola[7], Sara Monti[8], Chiara Marvisi[9], Alessandro Giollo[6], Lorenza M. Argolini[10], Matteo Righini[11], Angelica Gattamelata[12], Giulia Cassone[13], Laura Sottini[14], Matteo Maule[15], Paola Toniati[7], Bianca L. Palermo[3], Federica Bello[5], Silvia Guella[4], Raffaella Izzo[12], Francesco Muratore[9], Maria Grazia Catanoso[2], Angelo Fassio[15], Pierluigi Cataleta[11], Andrea Buscaroli[11], Marta Ottone[2], Paolo Giorgi Rossi[2], Franco Franceschini[7], Roberto Caporali[10], Carlomaurizio Montecucco[8], Fabrizio Conti[12], Giacomo Emmi[5], Luca Quartuccio[4], Giuseppe Paolazzi[14], Lorenzo Dagna[3], Franco Schiavon[6], Carlo Salvarani[9], Roberto Bortolotti[14].

[1]CISMED - University of Trento, Trento, Italy; [2]USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy; [3]UniRAR, San Raffaele Institute, Milan, Italy; [4]University of Udine, Udine, Italy; [5]University of Florence, Florence, Italy; [6]University of Padua, Padua, Italy; [7]University of Brescia, Brescia, Italy; [8]University of Pavia, Pavia, Italy; [9]University of Modena-Reggio Emilia, Reggio Emilia, Italy; [10]ASST G. Pini-CTO, Milan, Italy; [11]Ospedale S. Maria delle Croci, Ravenna, Italy; [12]Sapienza University, Rome, Italy; [13]University of Modena-Reggio Emilia, Modena, Italy; [14]APSS Trento, Trento, Italy; [15]University of Verona, Verona, Italy.

Background/ Objectives: To determine hospitalization rates and features in a large cohort of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: Hospitalization dates, features, length of stay, primary discharge diagnoses and patient data were abstracted from charts of AAV patients from 13 Italian hospitals, between 2007 and 2018. Age- and sex-standardized hospitalization rates (SHR) were calculated by an indirect method, per year and for the study period, using the 2007–2018 hospitalization data provided by the Italian Ministry of Health. Multivariable and survival models were used to explore associations between these outcomes, clinical parameters at diagnosis, and pre-existing comorbidities.

Results: A total of 610 hospitalizations occurred during follow up 47.1% of the 635 patients with AAV (19.4% microscopic polyangiitis, MPA; 34.6% granulomatosis with polyangiitis, GPA; 46.0% eosinophilic GPA, EGPA) during a 12-year observation; in 19.8% for life-threatening conditions and leading to death in 2.3%. The median hospitalization length was 8 days (25-75%IQR, 8-14).



These rates of hospitalization were stably higher in AAV and GPA, MPA and EGPA subsets as compared to general population (2018 SHR (95%CI) for AAV: 1.64 (1.35, 1.97); **Figure 1A:** Age- and sex-SHR by year during 2007-2018).

The main causes of hospitalization in patients with AAV were infectious diseases (18.7%), followed by major relapse and diagnostic re-evaluation (17.2% each), and cardiovascular diseases (10.8%). Among AAV patients hospitalized during follow-up, 55.5% had only 1 hospitalization, 18.7% had 2, and 25.6% had 3 or more hospitalizations. Patients with a diagnosis of GPA or MPA (versus EGPA), higher vasculitis activity (assessed by BVAS), ANCA positivity at diagnosis, and hospitalization at diagnosis ($p<0.001$), more pre-existing comorbidities and older age ($p<0.05$), were more likely to be hospitalized during follow-up (**Figure 1B:** Kaplan-Meier plots of the probability of hospitalization after AAV diagnosis). In a multivariate model, only GPA diagnosis (b coefficient (2.5%-97.5% CI): 0.564 (0.258-0.871)) and higher BVAS at diagnosis (0.038 (0.017-0.058)) were independent predictors of hospitalization during follow-up (both $p<0.0001$).

Conclusions: Patients with AAV experience higher rates of hospitalization than the general population. Approximately half of the patients is hospitalized during follow-up, with identified risk profiles of patients more likely to be hospitalized, requiring more active vigilance.

References: Wallace, Z. et al. Arthritis Care Res. 2016.

Disclosures: SS worked at the IRCCS San Raffaele Scientific Institute at the time of the study and is now an employee of Bristol Myers Squibb.

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Overlapping Forms of Eosinophilic Granulomatosis with Polyangiitis and Granulomatosis with Polyangiitis: Presentation, Management and Outcomes

Federica Pallotti[1], Camille Mettler[2], Roberto Padoan[3], Francesca Regola[4], Franco Franceschini[5], Sergey Moiseev[6], Pavel Novikov[7], Mario Andrea Piga[8], Gianluca Moroncini[9], Silke Brix[10], Abdul Hadi Kafagi[11], Samuel Deshayes[12], Achille Aouba[12], Julien Campagne[13], Paolo Delvino[14], Jan Willem Cohen Tervaert[15], Luisa Brussino[16], Martin Michaud[17], Nils Venhoff[18], Federico Alberici[19], Claudia Iannone[20], Sophie Rosenstingl[21], Marin Moutel[22], Jean-Marc Galempoix[23], Vincent Cottin[24], Clara Jaccard[25], Diane Riehl[26], Paul Legendre[27], Anne-Claire Billet[28], Paola Parronchi[29], Luca Quartuccio[30], Vítor Silvestre Teixeira[31], Allyson Egan[32], David Jayne[32], Enrico Tombetti[33], Marco Caminati[34], Christian Pagnoux[35], Alexis Régent[36], Marc Ruivard[37], Loïc Guillevin[38], Xavier Puéchal[36] and Benjamin Terrier[39], and the French Vasculities Study Group and European EGPA Study Group, [1]Internal Medicine, Centre Hospitalier Universitaire de Caen, Caen, France, [2]Département de Médecine Interne, Centre de Référence National pour les maladies auto-immunes systémiques rares, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris, France, [3]Department of Medicine DIMED, Division of Rheumatology, University of Padua, Padua, Italy, [4]Unit of Rheumatology and Clinical Immunology, ASST Spedali Civili Brescia and University of Brescia, Brescia, Italy, [5]Scleroderma Unit, Rheumatology and Clinical Immunology Unit, ERN ReCONNET, ASST Spedali Civili, Brescia, Italy, Brescia, Italy, [6]Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia, [7]Sechenov First Moscow State Medical University, Moscow, Russia, [8]Postgraduate School of Allergy and Clinical Immunology, Università Politecnica delle Marche, Ancona, Italy, [9]Department of Clinical and Molecular Sciences, Marche Polytechnic University & Department of Internal Medicine, Marche University Hospital, Ancona, Italy, [10]Division of Cell Matrix Biology and Regenerative Medicine, School of Biological Sciences, The University of Manchester, Manchester, United Kingdom, [11]Division of Cardiovascular Sciences, School of Medical Sciences, University of Manchester, Manchester, United Kingdom, [12]Service d'immunologie clinique-médecine interne, CHU de Caen Normandie, Caen, France, [13]Hôpital Robert Schuman - Competence center for autoimmune diseases, Internal Medicine, Metz, France, [14]University of Milano-Bicocca, Milan, Milan, Italy, [15]University of Alberta, Edmonton, Canada, [16]SSDDU Immunologia Clinica ed Allergologia, AO Mauriziano, Turin, Italy, [17]Department of Internal Medicine, Clinique Saint-Exupery, Toulouse, France., Toulouse, France, [18]Medical Center - University of Freiburg, Internal Medicine, Department of Rheumatology and Clinical Immunology, Freiburg, Germany, [19]Nephrology Unit, ASST Spedali Civili di Brescia, Brescia, Italy, [20]Department of Rheumatology, University of Milan, and Rheumatology Department, ASST Pini-CTO, Milan, Italy, [21]Service Médecine Interne, Centre hospitalier intercommunal Compiègne Noyon, Compiègne Noyon, France, [22]Department of Internal Medicine, Infectious Diseases, and Clinical Immunology, Reims University Hospital, Reims, France, [23]J.M. Galempoix, MD, Department of Internal Medicine, Nord Ardennes Hospital, Charleville-Mézières, France, [24]Hôpital Louis Pradel, Centre de Référence des Maladies Pulmonaires Rares, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France, Lyon, France, [25]Gaston Bourret Hospital, Nouméa, New Caledonia, [26]Centre hospitalier intercommunal Toulon- La Seyne Sur Mer, Toulon, France, [27]Service Médecine Interne et Polyvalente, Centre Hospitaliers Le Mans, Le Mans, France, [28]Department of Internal Medicine, Édouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France, [29]University of Florence, Florence, Florence, Italy, [30]Division of Rheumatology, Department of Medicine, University of Udine, Udine, Italy, [31]Department of Rheumatology, Faro Hospital, Algarve, Portugal, [32]University of Cambridge, Cambridge, United

Kingdom, [33]Internal Medicine and Rheumatology, Department of Biomedical and Clinical Sciences, Sacco and Fatebenefratelli Hospitals, Milan, Italy, Milan, Italy, [34]Department of Medicine, Asthma, Allergy and Clinical Immunology Section, University of Verona, Verona, Italy, [35]Mount Sinai Hospital, Toronto, ON, Canada, [36]National Referral Center For Rare Systemic Autoimmune Diseases, Paris, France, [37]Internal Medicine Department, Estaing University Hospital, CHU Clermont-Ferrand, Clermonnt-Ferrand, Italy, [38]National Referral Center For Rare Systemic Autoimmune Diseases, Paris, Ile-de-France, France, [39]Service de Médecine interne, Hôpital Cochin, AP-HP, Paris, Ile-de-France, France

Meeting: ACR Convergence 2024

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SESSION INFORMATION

Date: Sunday, November 17, 2024

Session Type: Poster Session B

Title: Vasculitis – ANCA-Associated Poster II

Session Time: 10:30AM-12:30PM

Background/Purpose: ANCA-associated vasculitis (AAV) include granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (EGPA). Although these entities are often easily distinguished in daily practice, some cases may be more difficult to identify. Hence, the identification of overlapping forms between GPA and EGPA may be crucial due to different organ damage and therapeutic approaches. We aimed to describe the existence of overlapping forms of EGPA and GPA, phenotype, severity and therapeutic management.

Methods: We conducted a European multicenter retrospective study in 34 centers to include patients with overlapping forms of EGPA and GPA. Patients were defined as follows: 1) patients fulfilling both ACR/EULAR 2022 criteria for GPA and EGPA; 2) patients fulfilling ACR/EULAR 2022 criteria for EGPA with PR3-ANCA and/or pulmonary nodules; 3) patients fulfilling ACR/EULAR 2022 criteria for GPA with eosinophilic count >1000/mm^3; 4) patients with AAV who do not meet ACR/EULAR 2022 criteria for EGPA and GPA but have both PR3-ANCA and eosinophilia >1000/mm^3.

Results: A total of 137 patients with overlapping forms (males in 62.8%, median age 52.5 [IQR 42.2-63] years) were analyzed. The main clinical manifestations were constitutional symptoms (70.8%), ENT involvement (83.9%) (mainly sinusitis, nasal crusts or polyposis), lung nodules (55.5%) sometimes excavated, asthma (55.5%), alveolar hemorrhage (19.7%), cutaneous involvement (51.8%). Renal injury was observed in 48.2%, peripheral neuropathy in 39.4%, cardiac involvement in 24.1%, gastrointestinal involvement in 16.8% and central nervous system involvement in 8% (mainly ischemic stroke). ANCA were found in 80.3%, as PR3-ANCA in 61.3% and MPO-ANCA in 19%, and median eosinophil count was 6000/mm^3 [IQR 2500-10000]. Five factor score was ≥1 for 17 patients (12.4%). Induction therapy consisted of high-dose glucocorticoids in 134 patients (97.8%), preceded by methylprednisolone pulses in 47.4%, combined with cyclophosphamide in 42.3%, rituximab in 16.8%, plasma exchange in 8%, and mepolizumab in 2.2%. Remission was achieved in 93.4%, and maintenance therapy consisted in azathioprine (29.2%), methotrexate (13.9%), rituximab (12.4%) and mepolizumab (4.4%). Six (4.4%) more patients received mepolizumab during the follow-up. Relapse-free survival was 84.7% at 1 year and 54.7% at 5 years, and relapses occurred after a median of 24.9 months [IQR 8.5-47]. Relapses were mainly pulmonary in 55.4%, ENT in 45.9%, and neurological in 24.3%. In these EGPA/GPA forms, ENT signs was the only variable associated with relapse (OR 4.7 [1.3-19.8]), while age < 65 years, female, PR3-ANCA, and asthma tended to be not associated. Death occurred in 20 patients (14.6%).

Conclusion: Overlapping forms of EGPA and GPA may occur, sharing complications of both primary forms. Relapses seem to be frequent and mainly affect lungs, ENT and nerves. Rituximab has rarely been used in these forms despite the features of GPA, probably due to the frequent diagnosis of EGPA. A cluster analysis is underway to better characterize the patient population within this group and potentially different prognosis.

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Clinical science

Validation of the Italian version of the ANCA-associated vasculitis patient-reported outcome (AAV-PRO) questionnaire

Elena Treppo [1], Miriam Isola[2], Maria De Martino[2], Roberto Padoan[3], Alessandro Giollo [3], Maria Letizia Urban [4], Sara Monti [5,6], Silvia Sartorelli [7], Angelo Fassio [8], Lorenza Maria Argolini [9], Chiara Marvisi[10], Angelica Gattamelata[11], Francesca Regola [12], Francesco Ferro[13], Giulia Cassone[14], Francesca Motta[15], Alvise Berti [16], Edoardo Conticini [17], Serena Guiducci[18], Marco Matucci-Cerinic[18], Alberto Lo Gullo [19], Andreina Manfredi[14], Bruno Frediani[17], Roberto Bortolotti[16], Carlo Selmi[15,20], Chiara Baldini [13], Franco Franceschini[12], Fabrizio Conti[11], Roberto Caporali[9], Maurizio Rossini[8], Lorenzo Dagna[7], Carlomaurizio Montecucco[5,6], Giacomo Emmi[4,21], Franco Schiavon[3], Carlo Salvarani [10], Luca Quartuccio [1,*], on behalf of the Italian Study Group on Lung Involvement in Rheumatic Diseases and the Italian Vasculitis Study Group

[1]Division of Rheumatology, Department of Medicine, University of Udine, Udine, Italy
[2]Institute of Statistics, Department of Medicine, University of Udine, Udine, Italy
[3]Rheumatology Unit, Department of Medicine DIMED, University of Padua, Padova, Italy
[4]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[5]Department of Internal Medicine and Therapeutics, Università di Pavia, Pavia, Italy
[6]Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[7]IRCCS San Raffaele Scientific Institute, Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), Milano, Italy
[8]Rheumatology Unit, University of Verona, Verona, Italy
[9]Division of Clinical Rheumatology, ASST Istituto Gaetano Pini—CTO, Milano, Italy
[10]Azienda USL-IRCCS di Reggio Emilia and University of Modena and Reggio Emilia, Reggio Emilia, Italy
[11]Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Rheumatology Unit, Sapienza University of Rome, Rome, Italy
[12]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili, and Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[13]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[14]Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy
[15]Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center—IRCCS, Rozzano, Milano, Italy
[16]Center for Medical Sciences (CISMed), University of Trento, and Rheumatology Unit, Santa Chiara Hospital, APSS Trento, Italy
[17]Rheumatology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
[18]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Florence, Italy
[19]Rheumatology Unit, Garibaldi Hospital, Catania, Italy
[20]Department of Biomedical Sciences, Humanitas University, Milano, Italy
[21]Centre for Inflammatory Diseases, Monash University Department of Medicine, Monash Medical Centre, Clayton, Victoria, Australia

*Correspondence to: Luca Quartuccio, Clinica di Reumatologia, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Piazzale Santa Maria della Misericordia 15, 33100 Udine (UD), Italy. E-mail: luca.quartuccio@uniud.it

Abstract

Objectives: The primary objective of this study was the translation and validation of the ANCA-associated vasculitis patient-reported outcome (AAV-PRO) questionnaire into Italian, denoted as AAV-PRO_ita. The secondary objective was to evaluate the impact of ANCA-associated vasculitis (AAV) on quality of life (QoL) and work impairment in a large cohort of Italian patients.

Methods: The study design took a prospective cohort study approach. First, the AAV-PRO was translated into Italian following the step guidelines for translations. The new AAV-PRO_ita questionnaire covered three disease domains: organ-specific and systemic symptoms and signs; physical function; and social and emotional impact. Second, Italian-speaking AAV patients were recruited from 17 Italian centres belonging to the Italian Vasculitis Study Group. Participants completed the AAV-PRO_ita questionnaire at three time points. Participants were also requested to complete the work productivity and activity impairment: general health questionnaire.

Results: A total of 276 AAV patients (56.5% women) completed the questionnaires. The AAV-PRO_ita questionnaire demonstrated a good internal consistency and test–retest reliability. Female AAV patients scored higher (i.e. worse) in all thee domains, especially in the social and emotional impact domain ($P < 0.001$). Patients on glucocorticoid therapy ($n = 199$) had higher scores in all domains, especially in the physical function domain ($P < 0.001$), compared with patients not on glucocorticoid therapy ($n = 77$). Furthermore, patients who had at least one relapse

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of disease ($n = 114$) had higher scores compared with those who had never had one ($n = 161$) in any domain ($P < 0.05$). Finally, nearly 30% of the patients reported work impairment.

Conclusion: The AAV-PRO_ita questionnaire is a new 29-item, disease-specific patient-reported outcome measuring tool that can be used in AAV research in the Italian language. Sex, glucocorticoids and relapsing disease showed the greatest impact on QoL.

Lay Summary

What does this mean for patients?

Improved therapeutic strategies for ANCA-associated vasculitis (AAV) have transformed acute, life-threatening disease into more manageable, chronic disease. However, chronic disease still has an impact on AAV patients' quality of life (QoL), employment and work disability. We translated the AAV-PRO questionnaire (which collects data on patient-reported outcomes) into Italian. Two hundred and seventy-six AAV patients in Italy then completed the questionnaire. We found that biological sex, steroid use and relapsing disease had the biggest impact on patients' QoL. Research on treatment strategies based on a steroid-sparing regimen and an increased awareness of sex differences might improve the perceived QoL of AAV patients, reducing the psychosocial and work impact of this chronic disease. Our study emphasizes the usefulness of user-friendly, translated questionnaires in standardizing QoL and work disability data in different groups of AAV patients. Therefore, we advocate the widespread use of the AAV-PRO questionnaire globally. This approach would enable us to gather comprehensive data, ultimately facilitating a more tailored approach to care for AAV patients.

Keywords: AAV-PRO, ANCA, vasculitis, patient-reported outcome, quality of life, questionnaire, work impairment, glucocorticoids.

Key messages

- AAV-PRO_ita questionnaire is a disease-specific patient-reported outcome measuring tool with good internal consistency and test–retest reliability.
- Translated AAV-PRO questionnaires may be included routinely in the clinical evaluation of AAV patients worldwide.
- Sex, glucocorticoids and relapsing disease may influence the quality of life of patients.

Introduction

ANCA-associated vasculitis (AAV) is a group of systemic disorders involving small-sized blood vessel vasculitis [1, 2]. AAV is a rare disease and encompasses three different entities, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).

Considering the improved therapeutic strategies, AAV has evolved mainly from an acute and severe disease to a chronic one, and although the prognosis has improved greatly over the years, patients suffer from the long-term consequences of the disease and its treatment, which, although life-saving, is often associated with significant side effects [3]. Recent papers on AAV have underscored the importance of patient-reported outcomes (PROs) in routine medical evaluation and clinical trials [4]. Given that generic PROs can lack specificity, the OMERACT Vasculitis Working Group identified the need for an AAV-specific PRO to capture the perspective of patients fully. An international steering committee comprising patient partners, methodologists, statisticians and clinicians from the UK, USA and Canada developed and validated a new disease-specific PRO, in line with guidance from the US Food and Drug Administration [5, 6]. The ANCA-associated vasculitis patient-reported outcome (AAV-PRO) questionnaire is the new disease-specific PRO measure for AAV. It is a 29-item disease-specific PRO measure in the English language, proving to be valid, reliable, feasible and able to discriminate among disease states. AAV-PRO could become an extremely useful tool to support physicians in their choice of treatment and to investigate the point of view of patients on disease activity [7].

Methods

Objectives

The primary objective of this study was to translate and to assess the internal consistency, feasibility and reliability of the Italian version of the AAV-PRO questionnaire (AAV-PRO_ita).

The secondary purpose was to describe, for the first time, a large cohort of Italian AAV patients, by taking into account three disease domains in the questionnaire {organ-specific and systemic symptoms and signs (SSS); patients' difficulties in daily life [physical function (PF)]; and social and emotional impact (SEI), including concerns about the future} and by describing the impact of AAV on work productivity/impairment through the simultaneous administration of the work productivity and activity impairment: general health (WPAI: GH) questionnaire.

Study design

This study had a prospective multicentre observational cohort design. The study complied with established standards for translation, cross-cultural adaptation and validation of questionnaires, following the step guidelines for translations of the *Clinical Outcomes at Oxford University Innovation*. Endorsement from the Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK, University of Bristol School of Clinical Science, Bristol, UK and the University of Oxford, Nuffield Department of Population Health (HSRU), Oxford, UK was obtained.

Inclusion criteria and data collection

Participants had to have been diagnosed with AAV, be native speakers of Italian, be aged ≥18 years and fulfil the following conditions: confirming that they had AAV; having received either a positive test result for ANCA or a diagnostic biopsy or an angiogram; and currently or previously taking glucocorticoids or one or more other immunosuppressant.

The disease phenotype was defined according to the Chapel Hill Consensus nomenclature, and EGPA patients were also included. ANCA testing was done by standard IIF assay for cANCA and pANCA. PR3 and MPO testing was done by direct ELISA with commercially available kits at the local laboratory. The disease activity was evaluated using the BVAS version 3 (BVASv3). The disease damage was evaluated using vasculitis damage index (VDI). The baseline was

defined as time 0, corresponding to the first self-completed 29-item AAV-PRO_ita questionnaire.

Participants were recruited from 17 Italian centres with extensive experience in the diagnosis and treatment of systemic vasculitis, including AAV, and belonging to the Vasculitis Study Group of the Italian Society of Rheumatology. Participants were aware of the nature of the study, its purpose and procedures before they decide to participate.

Each AAV participant self-completed the 29-item AAV-PRO_ita candidate questionnaire during a clinical evaluation (time 0). Five to seven days after they provided baseline responses, participants were sent a repeat 29-item AAV-PRO_ita questionnaire (test–retest). Finally, after 3 months, all participants were again sent the same 29-item AAV-PRO_ita questionnaire. At baseline and after 3 months, AAV participants also self-completed the WPAI: GH questionnaire. The WPAI: GH questionnaire is available here: http://www.reillyassociates.net/WPAIGH__Italian-Italy_.pdf, and it allows researchers to examine the extent of absenteeism, presenteeism and impairment in daily activities [8].

Statistical analysis

Descriptive statistics included frequency analyses (percentages) for categorical variables and the mean (S.D.), median and interquartile range (IQR) for quantitative variables. Categorical variables were compared using the χ^2 test or Fisher's exact test, whereas continuous variables were compared using unpaired Student's *t*-test or the Mann–Whitney *U*-test for two groups, and one-way ANOVA or the Kruskal–Wallis test for more than two groups, according to the Shapiro–Wilk test establishing whether data were normally or non-normally distributed. Correlations between continuous variables and domain scores were assessed with Spearman's correlation coefficient (*r*). Regarding missing data, owing to the small percentage of this occurrence, statistics were carried out omitting the cases with missing values. All the analyses were assessed using StataCorp. 2023 (*Stata Statistical Software: Release 18*, StataCorp LLC, College Station, TX).

Additional details regarding the study procedures and sample size calculation are reported in the Supplementary Data S1, available at *Rheumatology Advances in Practice* online.

Compliance with ethical standards

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and the Department of Medicine Institutional Review Board (IRB) has approved the study (protocol no. 091/2021).

Results

Study population

A total of 276 participants were enrolled from 17 centres. The median age was 61 (IQR 51.5–71.6) months, and they were predominantly female (156, 56.5%). The types of AAV were GPA (146, 52.9%), EGPA (77, 27.9%) and MPA (53, 19.2%). The ANCA titre was still positive in 108 (39.1%) patients, whereas at disease onset ANCAs were positive in 247 (89.5%) patients [134 of 247 (54.3%) PR3/cANCA and 113 of 247 (45.8%) MPO/pANCA]. The median BVASv3 at baseline was 0 (IQR 0–3), whereas the median BVASv3 at the onset of the disease was 13 (IQR 8–18). Participants had a median illness duration of 62 (IQR 23.8–118.5) months. In their previous medical history, the percentages of patients who experienced at least one relapse, one hospitalization and one severe infection were 41.7, 53.3 and 22.1%, respectively. More than three-quarters of the patients (81.2%) were on immunosuppressant therapy, and 68.8% were still receiving a low dose of glucocorticoids. One hundred and fifty-five of 276 (56.2%) participants belonged to the working-age population, of whom 104 of 155 (67.1%) were in work (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online). Three of 276 participants died before completing the questionnaire at the third month owing to an infectious disease (two of three with severe acute respiratory syndrome coronavirus 2 infection and one of three with an unknown infection). Demographic and clinical characteristics of participants at baseline are shown in Table 1 and Fig. 1.

Measurement properties of AAV-PRO_ita questionnaire

The AAV-PRO_ita questionnaire was self-completed by all 276 participants at baseline, by 268 of 276 (97.1%)

Table 1. The demographic and clinical characteristics of survey participants at baseline (time 0)

Demographic characteristics	$n = 276$ (%)
Female	156 (56.5)
Male	120 (43.5)
Age, median (IQR), years	61 (51.5–71.6)
Age group	
≤45 years	44 (15.9)
>45, ≤60 years	93 (33.7)
>60, ≤75 years	99 (35.9)
>75 years	40 (14.5)
Ethnicity	
Caucasian	272 (98.5)
Asian	2 (0.7)
African-American	1 (0.4)
Hispanic	1 (0.4)
Type of AAV	
GPA	146 (52.9)
EGPA	77 (27.9)
MPA	53 (19.2)
BVASv3, median (IQR)	0 (0–3)
VDI, median (IQR)	2 (1–4)
On glucocorticoid therapy	199 (72.1)
On immunosuppressant therapy	224 (81.2)
Rituximab ($n = 224$)	73 (32.6)
Methotrexate ($n = 224$)	60 (26.8)
Azathioprine ($n = 224$)	43 (19.2)
Mycophenolate Mofetil ($n = 224$)	23 (10.3)
Cyclophosphamide ($n = 224$)	5 (2.2)
Others ($n = 224$)	20 (8.9)
Time from diagnosis, median (IQR), months	62 (23.8–118.5)
Number of relapses of disease	
0	161 (58.3)
1	69 (25)
≥2	46 (16.7)
Number of hospitalizations	
0	129 (46.7)
1	107 (38.8)
≥2	40 (14.5)
Number of severe infectious	
0	215 (77.9)
1	50 (18.1)
≥2	11 (4)
Working-age patients	155 (56.2)
Employed patients ($n = 155$)	104 (67.1)

AAV: ANCA-associated vasculitis; BVASv3: BVAS version 3; GPA: granulomatosis with polyangiitis; IQR: interquartile range; MPA: microscopic polyangiitis; VDI: vasculitis damage index.

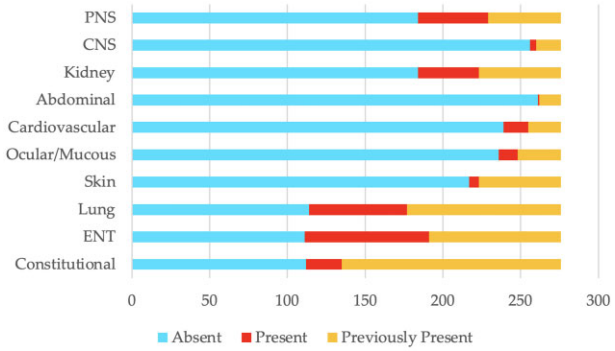

Figure 1. Clinical domains of Italian cohort of ANCA-associated vasculitis patients at baseline $n = 276$. AAV: ANCA-associated vasculitis; CNS: central nervous system; PNS: peripheral nervous system; ENT: ear, nose, throat

participants after 5–7 days, and by 266 of 273 (97.4%) participants at month 3.

The rate of missing response was 1.8% (432 missing responses out of a total of 23 925 questions). Cronbach's α ranged from 0.81 to 0.93 (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). The test–retest reliability was 0.95 (95% CI: 0.93, 0.96), 0.94 (95% CI: 0.93 0.95) and 0.95 (95% CI: 0.94, 0.96) in the three disease domains of the questionnaire, respectively (Supplementary Table S2, available at *Rheumatology Advances in Practice* online). The responses to the 29 items at baseline, divided into the three disease domains (SSS, PF and SEI) are shown in Fig. 2.

Comparison between the AAV-PRO_ita domain scores and demographic and clinical features

There were statistically significant associations between sex, current CS therapy, previous disease relapse and higher scores at baseline. In detail, scores for female patients were higher than those for male patients in all domains (SSS: $P = 0.047$; PF: P-value $= 0.005$; SEI: $P < 0.001$). There were also differences between patients on CS therapy ($n = 199$) and patients without CS therapy ($n = 77$); in fact, the former had higher scores in all domains (SSS: $P = 0.03$; PF: $P < 0.001$; SEI: P-value $= 0.005$). Furthermore, patients who had at least one relapse of the disease ($n = 114$) had higher scores compared with those who had never had one ($n = 161$) (SSS: $P = 0.013$; PF: $P = 0.015$; SEI: $P = 0.029$). No associations were found between CS therapy and previous relapses ($P = 0.550$) or between CS therapy and previous severe infectious ($P = 0.217$).

In contrast, there were no differences in median scores between younger and older responders and across AAV subtypes (GPA, MPA and EGPA). Disease duration, previous hospitalizations and/or infections, BVASv3 and VDI at baseline did not influence the scores. The statistical values for continuous variables are shown in Supplementary Table S3 and the statistical values for non-continuous variables in Supplementary Table S4, both available at *Rheumatology Advances in Practice* online.

Work productivity and activity impairment: general health questionnaire

Among the 104 working participants, 86 of 104 completed the WPAI: GH questionnaire at baseline and 83 of 104 at the third month. At baseline and at month 3, the percentage of absenteeism was 15% (S.D. 30%) and 8% (S.D. 23%), respectively. In other words, patients were absent from work on average 6 and 3 h per week. The percentage of presenteeism was 22% (S.D. 27%) both at baseline and at month 3. The percentage of overall work impairment was 30% (S.D. 31%) (at baseline) and 27% (S.D. 29%) (at month 3), and the percentage of activity impairment was 36% (S.D. 30%) (both at baseline and at month 3).

Considering the WPAI: GH questionnaire at baseline, the percentage of activity impairment was correlated with a higher score in the PF domain of AAV-PRO_ita [Spearman's correlation coefficient ($r > 0.7$ is strong correlation), $r = 0.72$, $P < 0.001$] and with the ongoing use of CS therapy ($P = 0.023$).

Discussion

The AAV-PRO_ita is a new 29-item, disease-specific PRO measure useful in AAV research in the Italian language. This study describes the underlying structure of the final AAV-PRO_ita. It has three disease domains that investigate the impact of symptoms, patients' difficulties related to physical function and their concerns in daily life. Each domain had good internal consistency (Cronbach's α ranged from 0.81 to 0.93) and good test–retest reliability (intraclass correlation coefficients ranged from 0.94 to 0.95). Item response rates were high overall (maximum of 1.8% missing data), supporting the feasibility of the questionnaire.

The female sex scored higher (i.e. worse) in all three domains, especially the SEI domain ($P < 0.001$), in all three stages of questionnaire self-completions (at baseline, after 5–7 days and after 3 months) (Fig. 3). The scores were not influenced by AAV phenotype or disease duration. These results are comparable to those found by Robson *et al.* [6], thus supporting the validity of a sex-based approach in AAV research [9]. Considering that disease activity was similar in our cohort [BVASv3: 0 (IQR 0–3)], the differences observed between sexes might have a clinically meaningful impact. Recognizing the emotional and psychological aspects of living with a chronic disease and promoting open and effective communication between health-care providers and female patients could serve as an example of a sex-based approach. In addition to classical treatment strategies, integrating psychological therapy into the care plan could provide essential emotional support, aid in accepting the chronic nature of the condition and help patients to deal with the unique psychological aspects of their journey. Health-care providers should also stay informed about the research related to sex-specific considerations in chronic disease management. First, not all patients with the same chronic disease will have identical experiences, as exemplified by differences in the perception of chronic pain among men and women; this diversity should be taken into account [10]. Second, sex also contributes to biological differences in innate and adaptative immunity. Recent evidence shows that biologics that stimulate immune function (e.g. vaccines) are generally more efficacious in females than males, and therapies that repress immunity (e.g. checkpoint inhibitors and TNF inhibitors) are more effective in males than females [11].

Current treatment and previous relapses also influenced the results of the questionnaire. Patients on CS therapy and those who experienced at least one relapse of the disease had higher scores in all domains. These findings had not been investigated in the previous validation study of the English

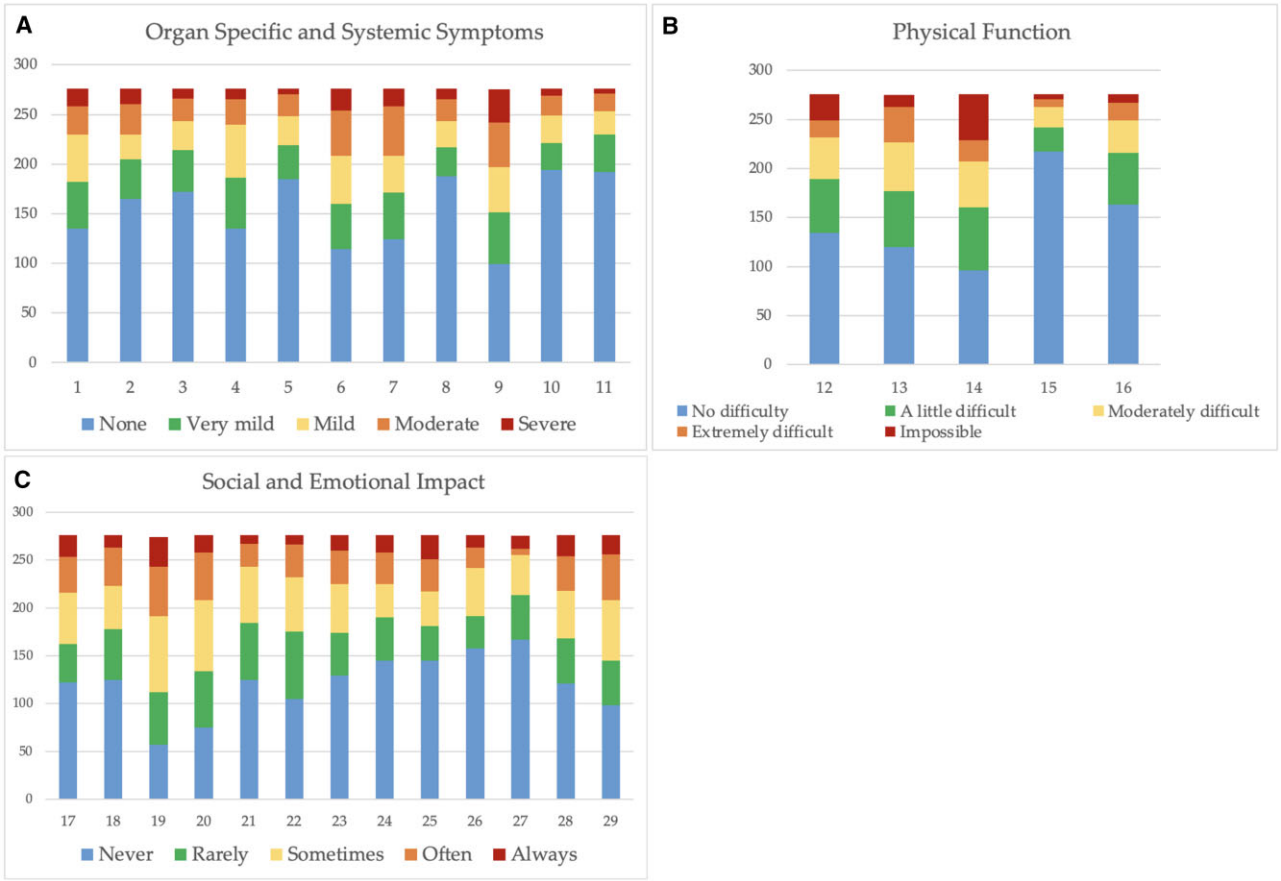

Figure 2. Survey responses at baseline for the 29 items. The *y*-axis shows the number of patients ($n = 276$). The *x*-axis shows the questionnaire items. (**A**) Organ-specific and systemic symptoms and signs. (**B**) Physical function. (**C**) Social and emotional impact

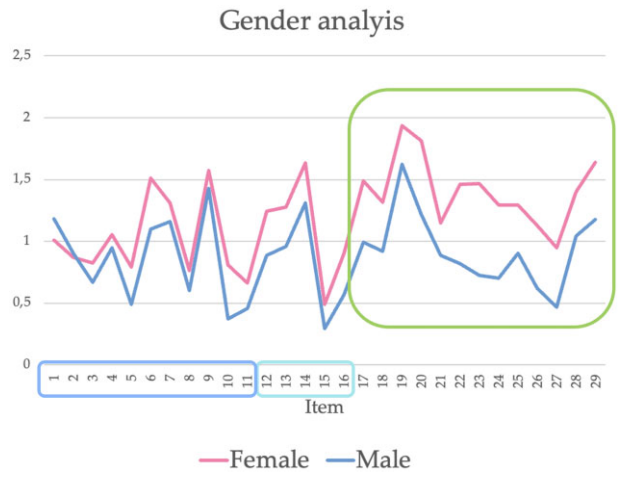

Figure 3. Representation of the mean scores of females and males for each item of the AAV-PRO_ita questionnaire $n = 276$. Light blue frame: organ-specific and systemic symptoms and signs (items 1–11); turquoise frame: physical function (items 12–16); green frame: social and emotional impact (items 17–29)

questionnaire [6]. Conversely, in the validation study of the English questionnaire [6] and in the preliminary evaluation of our questionnaire [12], older participants (≥65 years old) had higher scores in the PF domain ($P < 0.05$), and younger participants (<65 years old) showed a trend of higher scores in the SEI domain; however, these data were not confirmed by our final results. The VDI and BVASv3 did not appear to be related to the AAV-PRO_ita scores ($r < 0.3$, i.e. weak correlation), suggesting that the perspective of physicians and patients might be very different [7]. This lack of correlation was also confirmed recently by another study [13], encouraging the role of AAV-PRO as an additional and complementary endpoint to traditional clinical instruments (i.e. BVAS and VDI) in clinical trials [14]. It might be assumed that patients who required more CS therapy had a more severe disease; however, both VDI and immunosuppressant therapy were not associated with worse AAV-PRO_ita scores. Given the remission status or low disease activity within the cohort, the doses of glucocorticoids were low, making it impractical to categorize patients based on low, medium or high CS doses. Furthermore, there were no associations between ongoing CS therapy and previous relapses. Adverse effects related to glucocorticoid therapy are also likely to be connected to this finding, further emphasizing the global need for a new CS-sparing approach in AAV.

A recent review [15] highlighted that patients with vasculitis are most affected physically by fatigue, psychologically by anxiety, socially by reduced social participation and financially by functional decline and reduced employment. Furthermore, a recent Mexican study [16] reported that worries about the future scored highest on the Spanish-translated version of the AAV-PRO questionnaire. These findings also emerged in the AAV-PRO_ita questionnaire. Globally, our Italian questionnaire revealed patients' concerns about

general life issues (item 20), the future (item 19) and long-term treatment (item 29). More than half of patients claimed to be sometimes, often or always worried about the future (58.7%; item 19), about the effects of treatment (47.5%; item 29) and being on the whole stressed (51.5%; item 20) at baseline (Fig. 2). Overall, the SEI domain obtained the highest scores, supporting a poorly investigated malaise in AAV patients. As in other systemic autoimmune diseases, the perception of the patient's QoL is most likely to be influenced by the chronicity of the disease. With new treatments and increased survival, AAV has largely become a chronic condition, with the resulting impact on patients' daily lives. Concerning the SSS domain, the main symptoms reported by patients were fatigue (item 9), arthralgia (item 6), myalgia (item 7) and dyspnoea (item 1). About one-third of patients classified their respiratory and muscle symptoms as mild, moderate or severe. Approximately 45% and 42% of patients complained of fatigue and arthralgia, respectively. In particular, nearly one-third of patients classified fatigue as moderate or severe, which indicates that it has a significant role in the psychosocial impact of this illness. Currently, there is no specific treatment for fatigue, and fatigue is not addressed in the current management guidelines [17], and this represents a case of unmet needs in AAV [7]. With regard to the PF (i.e. the second domain), one-third of patients found it impossible or extremely difficult to engage in sport or physical activity (item 14). Furthermore, in a sub-analysis, no significant association was observed between higher scores in the PF domain and the presence of residual neuropathic damage ($P = 0.383$). These results highlight the influence and importance of both clinical and bio-psychosocial factors in the perception of life quality.

The impact of work disability is another interesting aspect of AAV deserving further attention. Overall, there were 155 working-age patients, but only 67.1% of them worked. It is likely that AAV might have played a role in this employment rate [18, 19]. A recent Australian study, in which the WPAI: specific health problem questionnaire was administered in 47 AAV patients, reported that ∼25% of responders left paid employment owing to their illness and almost 50% of patients had their financial status impacted [19]. Heron *et al.* [19] found a rate of work disability of 23.4% and observed how work impairment was associated with obesity, lower education and fatigue [20]. Similar to our data, the Australian authors did not find a correlation between BVASv3 and VDI. However, there is no widely accepted definition of work disability; thus, the methods for measuring work disability vary from study to study, making direct comparison between studies and patient groups difficult. Furthermore, to date, few published studies have investigated the impact of work disability in a patient population with systemic vasculitis. In a recent French study, the EXPOVAS study [18], which included 94 patients, the rate of work disability was as high as 40%. An online survey-based study [21] involving 421 North American AAV patients found that 26% of participants became permanently unable to work or had to retire early owing to vasculitis, and the reported mean productivity loss was 7%. In the Australian AAV cohort [19], 10.1% of patients reported missing work in the previous week. This figure is similar to that of our Italian cohort, where absenteeism was ∼8–15% across the two questionnaire completions. The

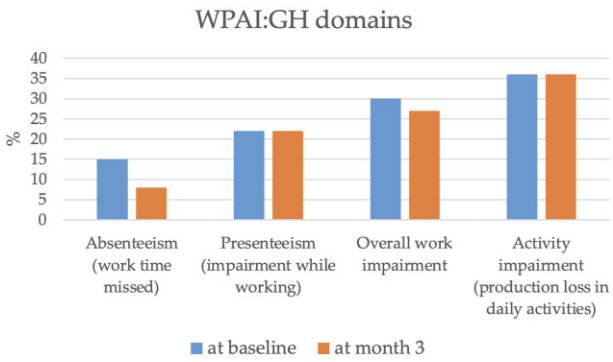

Figure 4. Work productivity and activity impairment (general health) questionnaire in our cohort of ANCA-associated vasculitis patients. WPAI: GH: work productivity and activity impairment (general health)

mean activity impairment from our cohort and the Australian cohort was 36% (S.D. 30%) and 26.4% (S.D. 23.6%), respectively. In our study, the percentage of activity impairment seemed to be related to ongoing CS therapy, suggesting once again that CS-sparing approaches could improve AAV management and patients' QoL. It is also interesting to compare work inability in AAV with that of other rheumatic diseases, such as chronic arthritis. In a previous paper [22], in which the WPAI: GH questionnaire had been administered to a group of Czech patients with arthritis, absenteeism ranged from 8% of patients with RA to 10% of patients with AS, reaching a peak of 20% in patients with PsA owing to the time-consuming treatment and care involved (e.g. phototherapy). Compared with RA and AS, the loss of productivity in our cohort appeared to occur to a lesser extent [22] (Fig. 4). It could be assumed that arthritis influences work productivity more owing to physical impairment. However, neither a DAS in 28 joints [22] nor BVASv3 seemed to be correlated with WPAI: GH. In contrast, the HAQ and the PF domain of the Italian AAV-PRO_ita questionnaire proved to be correlated with work impairment in RA and AAV, respectively. The association between the PF domain of AAV-PRO_ita and work impairment tested by WPAI: GH corroborates the validity of our results. These data suggest an additional evaluation of the impact of the AAV disease on work activity. Further investigation is required to explore this interesting topic and to investigate further the issue of the QoL in AAV patients.

Strengths and limitations

This study has several strengths. It benefits from a robust sample size, allowing for a comprehensive and statistically meaningful assessment of the performance of the questionnaire. The large number of patients enhances the generalizability of the findings obtained. Additionally, the rigorous methodology adopted in the validation process ensures the reliability and validation of the questionnaire in assessing QoL among AAV patients and helps to clarify which factors might influence it. Furthermore, the absence of an association between the AAV-PRO_ita questionnaire and current clinician instruments, namely VDI and BVAS, supports the idea that this questionnaire complements the overall assessment of AAV patients.

Although the study demonstrates several strengths, it is not without limitations. Potential limitations are the missing data within the cohort and the design of the study. First, missing data arise from non-response by some participants, introducing a bias in the completeness of the analysis. Second, the study might provide a snapshot of the QoL but not capture the dynamic changes that can occur over time. Nevertheless, it is worth noting that the rate of missing response was low, and further studies can deepen the understanding of variations in the perception of life within AAV cohorts over time.

Conclusions

The AAV-PRO_ita is a new 29-item, disease-specific PRO measure to be used in AAV research in the Italian language. It is a self-administered Italian questionnaire with a good internal consistency, feasibility and reliability. AAV-PRO_ita proved to be a useful tool to explore the perception by AAV patients of their QoL, and it could become an important way of measuring the unmet needs of AAV patients. Nowadays, concerns in daily life seem greatly to influence the health-related QoL of AAV patients, especially in female and working patients. Loss of employment and capacity to work is likely to contribute to loss of one's status in society, social status and adverse economic consequences for individuals and society at large. These findings also support the validity of research on treatment strategies based on a CS-sparing regimen, showing that patients on a chronic CS therapy had a negative perception of their QoL and working life. Moreover, as with other systemic autoimmune diseases, the problems of fatigue and chronic pain still represent an open challenge for physicians.

This study argues for the need to use validated and user-friendly questionnaires on both QoL and work impairment in order to standardize the results obtained in the different cohorts of AAV patients. In particular, the AAV-PRO questionnaire is easy to use, self-administered, and its translations could be disseminated and included routinely in worldwide clinical evaluation of AAV patients.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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References

1. Jennette JC, Falk RJ, Bacon PA *et al.* 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1–11.
2. Geetha D, Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. Am J Kidney Dis 2020;75:124–37.
3. Quartuccio L, Treppo E, Valent F, De Vita S. Healthcare and economic burden of ANCA-associated vasculitis in Italy: an integrated analysis from clinical and administrative databases. Intern Emerg Med 2020;16:581–9.
4. Crawshaw H, Wells M, Austin K, Janagan S, Robson JC. Patient reported outcomes in systemic vasculitis. Curr Opin Rheumatol 2022;34:33–8.
5. Robson JC, Milman N, Tomasson G *et al.* Exploration, development, and validation of patient-reported outcomes in antineutrophil cytoplasmic antibody-associated vasculitis using the OMERACT process. J Rheumatol 2015;42:2204–9.
6. Robson JC, Dawson J, Doll H *et al.* Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire. Ann Rheum Dis 2018;77:1157–64.
7. Quartuccio L, Treppo E, Urso L *et al.* Unmet needs in ANCA-associated vasculitis: physicians' and patients' perspectives. Front Immunol 2023;14:1112899.
8. Tang K, Beaton DE, Boonen A, Gignac MAM, Bombardier C. Measures of work disability and productivity: Rheumatoid Arthritis Specific Work Productivity Survey (WPS-RA), Workplace Activity Limitations Scale (WALS), Work Instability Scale for Rheumatoid Arthritis (RA-WIS), Work Limitations Questionnaire (WLQ), and Work Productivity and Activity Impairment Questionnaire (WPAI). Arthritis Care Res 2011;63(Suppl 11):S337–349.
9. Zhu Q, Li F, Xie X *et al.* Relationship between gender and 1-year mortality in ANCA-associated vasculitis patients: a single-center retrospective analysis and meta-analysis. Front Med 2022; 9:945011.
10. Samulowitz A, Gremyr I, Eriksson E, Hensing G. 'Brave men' and 'emotional women': a theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain. Pain Res Manag 2018;2018:6358624.
11. Klein SL, Morgan R. The impact of sex and gender on immunotherapy outcomes. Biol Sex Differ 2020;11:24.
12. Treppo E, Isola M, Martino MD *et al.* AB0627 Evaluation of internal consistency, feasibility, and reliability of the Italian version of ANCA-associated vasculitis patient-reported outcome (AAV-PRO_ita) questionnaire: preliminary results from a multicenter study on a large cohort of Italian patients. Ann Rheum Dis 2022; 81:1440.
13. Maunz A, Jacoby J, Henes J *et al.* Association of the AAV-PRO questionnaire with established outcome measures in AAV. Rheumatology (Oxford) 2024;63:174–80.
14. Berti A, Boleto G, Merkel PA *et al.* Psychometric properties of outcome measurement instruments for ANCA-associated vasculitis: a systematic literature review. Rheumatology (Oxford) 2022; 61:4603–18.
15. Gill N, Tervaert JWC, Yacyshyn E. Vasculitis patient journey: a scoping review of patient experiences with vasculitis. Clin Rheumatol 2021;40:1697–708.
16. Hurtado-Arias JJ, Ramírez-Mulhern I, Gonzalez-Martínez C *et al.* Patient-reported outcomes in ANCA-associated vasculitis: a cross-sectional study to explore the interactions between patients' and physicians' perspectives. Rheumatol Int 2023;43:933–40.
17. Yates M, Watts RA, Bajema IM *et al.* EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.
18. Benarous L, Terrier B, Laborde-Casterot H *et al.* Employment, work disability and quality of life in patients with ANCA-associated vasculitides. The EXPOVAS study. Clin Exp Rheumatol 2017;35(Suppl 103):40–6.

19. Heron V, Gingold M, Kitching AR, Polkinghorne KR, Ryan J. The impact of antineutrophil cytoplasmic antibody-associated vasculitis on employment and work disability in an Australian population. Int J Rheum Dis 2021;24:904–11.
20. Basu N, McClean A, Harper L *et al.* Markers for work disability in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatology (Oxford) 2014;53:953–6.
21. Barra L, Borchin RL, Burroughs C *et al.* Impact of vasculitis on employment and income. Clin Exp Rheumatol 2018;36(Suppl 111):58–64.
22. Kruntorádová K, Klimeš J, Šedová L *et al.* Work productivity and costs related to patients with ankylosing spondylitis, rheumatoid arthritis, and psoriasis. Value Health Reg Issues 2014; 4:100–6.

REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1–11.

2. Tomasson G, Bjornsson J, Zhang Y, Gudnason V, Merkel PA. Cardiovascular risk factors and incident giant cell arteritis: a population-based cohort study. Scand J Rheumatol 2019;48:213–7.

3. Mohammad AJ, Nilsson JÅ, Jacobsson LTH, Merkel PA, Turesson C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. Ann Rheum Dis 2015;74:993–7.

4. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. Ann Intern Med 1995;123:192–4.

5. Kobayashi S, Yano T, Matsumoto Y, Numano F, Nakajima N, Yasuda K, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. Arthritis Rheum 2003;49:594–8.

6. Pamuk ON, Dönmez S, Karahan B, Pamuk GE, Cakir N. Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: Clinical features and epidemiological data. Clin Exp Rheumatol 2009;27:830–3.

7. Catanoso M, Macchioni P, Boiardi L, Muratore F, Restuccia G, Cavazza A, et al. Incidence, Prevalence, and Survival of Biopsy-Proven Giant Cell Arteritis in Northern Italy During a 26-Year Period. Arthritis Care Res (Hoboken) 2017;69:430–8.

8. Muratore F, Boiardi L, Mancuso P, Restuccia G, Galli E, Marvisi C, et al. Incidence and prevalence of large vessel vasculitis (giant cell arteritis and Takayasu

arteritis) in northern Italy: A population-based study. Semin Arthritis Rheum 2021;51:786–92.

9. Carmona FD, Mackie SL, Martín JE, Taylor JC, Vaglio A, Eyre S, et al. A Large-Scale Genetic Analysis Reveals a Strong Contribution of the HLA Class II Region to Giant Cell Arteritis Susceptibility. The American Journal of Human Genetics 2015;96:565–80.

10. Carmona FD, Vaglio A, Mackie SL, Hernández-Rodríguez J, Monach PA, Castañeda S, et al. A Genome-wide Association Study Identifies Risk Alleles in Plasminogen and P4HA2 Associated with Giant Cell Arteritis. The American Journal of Human Genetics 2017;100:64–74.

11. Hysa E, Sobrero A, Camellino D, Rumi F, Carrara G, Cutolo M, et al. A seasonal pattern in the onset of polymyalgia rheumatica and giant cell arteritis? A systematic review and meta-analysis. Semin Arthritis Rheum 2020;50:1131–9.

12. Nagel MA, White T, Khmeleva N, Rempel A, Boyer PJ, Bennett JL, et al. Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis. JAMA Neurol 2015;72:1281–7.

13. Cid MC, Campo E, Ercilla G, Palacin A, Vilaseca J, Villalta J, et al. Immunohistochemical analysis of lymphoid and macrophage cell subsets and their immunologic activation markers in temporal arteritis. Influence of corticosteroid treatment. Arthritis Rheum 1989;32:884–93.

14. Ma-Krupa W, Jeon MS, Spoerl S, Tedder TF, Goronzy JJ, Weyand CM. Activation of Arterial Wall Dendritic Cells and Breakdown of Self-tolerance in Giant Cell Arteritis. The Journal of Experimental Medicine 2004;199:173–83.

15. Espígol-Frigolé G, Corbera-Bellalta M, Planas-Rigol E, Lozano E, Segarra M, García-Martínez A, et al. Increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with giant-cell arteritis. Ann Rheum Dis 2013;72:1481–7.

16. Ciccia F, Rizzo A, Maugeri R, Alessandro R, Croci S, Guggino G, et al. Ectopic expression of CXCL13, BAFF, APRIL and LT-β is associated with artery tertiary lymphoid organs in giant cell arteritis. Ann Rheum Dis 2017;76:235–43.

17. Wagner AD, Goronzy JJ, Weyand CM. Functional profile of tissue-infiltrating and circulating CD68+ cells in giant cell arteritis. Evidence for two components of the disease. J Clin Invest 1994;94:1134–40.

18. Dasgupta B, Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol 1990;29:456–8.

19. Kaiser M, Younge B, Björnsson J, Goronzy JJ, Weyand CM. Formation of new vasa vasorum in vasculitis. Production of angiogenic cytokines by multinucleated giant cells. Am J Pathol 1999;155:765–74.

20. Rittner HL, Kaiser M, Brack A, Szweda LI, Goronzy JJ, Weyand CM. Tissue-destructive macrophages in giant cell arteritis. Circ Res 1999;84:1050–8.

21. Samson M, Ly KH, Tournier B, Janikashvili N, Trad M, Ciudad M, et al. Involvement and prognosis value of CD8(+) T cells in giant cell arteritis. J Autoimmun 2016;72:73–83.

22. Segarra M, García-Martínez A, Sánchez M, Hernández-Rodríguez J, Lozano E, Grau JM, et al. Gelatinase expression and proteolytic activity in giant-cell arteritis. Ann Rheum Dis 2007;66:1429–35.

23. Lozano E, Segarra M, García-Martínez A, Hernández-Rodríguez J, Cid MC. Imatinib mesylate inhibits in vitro and ex vivo biological responses related to vascular occlusion in giant cell arteritis. Ann Rheum Dis 2008;67:1581–8.

24. Calamia KT, Hunder GG. Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. Arthritis Rheum 1981;24:1414–8.

25. Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. J Am Geriatr Soc 1993;41:1187–92.

26. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 1985;254:2763–7.

27. Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, Garcia-Porrua C, Sanchez-Andrade A, Llorca J. Giant Cell Arteritis: Disease Patterns of Clinical Presentation in a Series of 240 Patients. Medicine 2005;84:269–76.

28. Gabriel SE, O'Fallon WM, Achkar AA, Lie JT, Hunder GG. The use of clinical characteristics to predict the results of temporal artery biopsy among patients with suspected giant cell arteritis. J Rheumatol 1995;22:93–6.

29. Helfrich DJ, Mulhern LM, Luparello FJ, Smith W. Giant cell arteritis of the tongue presenting as macroglossia. J Rheumatol 1988;15:1026–8.

30. Tsianakas A, Ehrchen JM, Presser D, Fischer T, Kruse-Loesler B, Luger TA, et al. Scalp necrosis in giant cell arteritis: case report and review of the relevance of this cutaneous sign of large-vessel vasculitis. J Am Acad Dermatol 2009;61:701–6.

31. Brodmann M, Dorr A, Hafner F, Gary T, Pilger E. Tongue necrosis as first symptom of giant cell arteritis (GCA). Clin Rheumatol 2009;28 Suppl 1:S47-49.

32. Liozon E, Dalmay F, Lalloue F, Gondran G, Bezanahary H, Fauchais AL, et al. Risk Factors for Permanent Visual Loss in Biopsy-proven Giant Cell Arteritis: A Study of 339 Patients. J Rheumatol 2016;43:1393–9.

33. Nesher G, Nesher R, Mates M, Sonnenblick M, Breuer GS. Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease. Clin Exp Rheumatol 2008;26:S30-34.

34. Jonasson F, Cullen JF, Elton RA. Temporal Arteritis: A 14-Year Epidemiological, Clinical and Prognostic Study. Scott Med J 1979;24:111–7.

35. Vodopivec I, Rizzo JF. Ophthalmic manifestations of giant cell arteritis.

Rheumatology (Oxford) 2018;57:ii63–72.

36. Razavi M, Jones RD, Manzel K, Fattal D, Rizzo M. Steroid-Responsive Charles Bonnet Syndrome in Temporal Arteritis. JNP 2004;16:505–8.

37. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, Pego-Reigosa R, Lopez-Diaz MJ, Vazquez-Triñanes MC, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore) 2009;88:227–35.

38. Turney TM, Garraway WM, Whisnant JP. The natural history of hemispheric and brainstem infarction in Rochester, Minnesota. Stroke 1984;15:790–4.

39. Armellin L, Sammel AM, Ng B, Sarathy K, Lambros J, Amir-Nezami T, et al. Coronary artery stenting in acute coronary syndrome associated with giant cell arteritis. J Cardiol Cases 2017;16:77–81.

40. Scola CJ, Li C, Upchurch KS. Mesenteric Involvement in Giant Cell Arteritis. An Underrecognized Complication?: Analysis of a Case Series With Clinicoanatomic Correlation. Medicine 2008;87:45–51.

41. Evans JM, Bowles CA, Bjornsson J, Mullany CJ, Hunder GG. Thoracic aortic aneurysm and rupture in giant cell arteritis. A descriptive study of 41 cases. Arthritis Rheum 1994;37:1539–47.

42. Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis 2013;72:1989–94.

43. Kebed DT, Bois JP, Connolly HM, Scott CG, Bowen JM, Warrington KJ, et al. Spectrum of Aortic Disease in the Giant Cell Arteritis Population. Am J Cardiol 2018;121:501–8.

44. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. Ann Intern Med 1995;122:502–7.

45. Biousse V, Newman NJ. Ischemic Optic Neuropathies. N Engl J Med 2015;372:2428–36.

46. Gonzalez-Gay MA, Lopez-Diaz MJ, Barros S, Garcia-Porrua C, Sanchez-Andrade A, Paz-Carreira J, et al. Giant Cell Arteritis: Laboratory Tests at the Time of Diagnosis in a Series of 240 Patients. Medicine 2005;84:277–90.

47. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol 2021;73:1349–65.

48. Narváez J, Bernad B, Roig-Vilaseca D, García-Gómez C, Gómez-Vaquero C, Juanola X, et al. Influence of Previous Corticosteroid Therapy on Temporal Artery Biopsy Yield in Giant Cell Arteritis. Seminars in Arthritis and Rheumatism 2007;37:13–9.

49. Jia L, Couce M, Barnholtz-Sloan JS, Cohen ML. Is all inflammation within temporal artery biopsies temporal arteritis? Human Pathology 2016;57:17–21.

50. Cavazza A, Muratore F, Boiardi L, Restuccia G, Pipitone N, Pazzola G, et al. Inflamed Temporal Artery: Histologic Findings in 354 Biopsies, With Clinical Correlations. American Journal of Surgical Pathology 2014;38:1360–70.

51. Chu R, Foster C, Ali M, Chaba T, Clifford AH, Mahr A, et al. Optimal length and usefulness of temporal artery biopsies in the diagnosis of giant cell arteritis: a 10-year retrospective review of medical records. Lancet Rheumatol 2020;2:e774–8.

52. Smetana GW. Does This Patient Have Temporal Arteritis? JAMA 2002;287:92.

53. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77:636–43.

54. Arida A, Kyprianou M, Kanakis M, Sfikakis PP. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC Musculoskelet Disord 2010;11:44.

55. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA 2016;315:2442–58.

56. Schäfer VS, Jin L, Schmidt WA. Imaging for Diagnosis, Monitoring, and Outcome Prediction of Large Vessel Vasculitides. Curr Rheumatol Rep 2020;22:76.

57. Lariviere D, Benali K, Coustet B, Pasi N, Hyafil F, Klein I, et al. Positron emission tomography and computed tomography angiography for the diagnosis of giant cell arteritis: A real-life prospective study. Medicine (Baltimore) 2016;95:e4146.

58. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.

59. Ponte C, Grayson PC, Robson JC, Suppiah R, Gribbons KB, Judge A, et al. 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis. Arthritis Rheumatol 2022;74:1881–9.

60. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.

61. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med 2017;377:317–28.

62. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. The Lancet 2016;387:1921–7.

63. Adler S, Reichenbach S, Gloor A, Yerly D, Cullmann JL, Villiger PM. Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis. Rheumatology 2019;58:1639–43.

64. Stone JH, Han J, Aringer M, Blockmans D, Brouwer E, Cid MC, et al. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. The Lancet Rheumatology 2021;3:e328–36.

65. Quinn KA, Dashora H, Novakovich E, Ahlman MA, Grayson PC. Use of 18F-fluorodeoxyglucose positron emission tomography to monitor tocilizumab effect on vascular inflammation in giant cell arteritis. Rheumatology 2021;60:4384–9.

66. Regola F, Cerudelli E, Bosio G, Andreoli L, Tincani A, Franceschini F, et al. Long-term treatment with tocilizumab in giant cell arteritis: efficacy and safety in a monocentric cohort of patients. Rheumatology Advances in Practice 2020;4:rkaa017.

67. Gérard AL, Simon-Tillaux N, Yordanov Y, Cacoub P, Tubach F, Saadoun D, et al. Efficacy and safety of steroid-sparing treatments in giant cell arteritis according to the glucocorticoids tapering regimen: A systematic review and meta-analysis. European Journal of Internal Medicine 2021;88:96–103.

68. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis & Rheumatology 2017;69:837–45.

69. Wilson JC, Sarsour K, Collinson N, Tuckwell K, Musselman D, Klearman M, et al. Serious adverse effects associated with glucocorticoid therapy in patients

with giant cell arteritis (GCA): A nested case–control analysis. Seminars in Arthritis and Rheumatism 2017;46:819–27.

70. Wu J, Keeley A, Mallen C, Morgan AW, Pujades-Rodriguez M. Incidence of infections associated with oral glucocorticoid dose in people diagnosed with polymyalgia rheumatica or giant cell arteritis: a cohort study in England. CMAJ 2019;191:E680–8.

71. Schmidt J, Smail A, Roche B, Gay P, Salle V, Pellet H, et al. Incidence of Severe Infections and Infection-Related Mortality During the Course of Giant Cell Arteritis: A Multicenter, Prospective, Double-Cohort Study. Arthritis & Rheumatology 2016;68:1477–82.

72. Hoon E, Ruediger C, Gill TK, Black RJ, Hill CL. A qualitative study of patient perspectives related to glucocorticoid therapy in polymyalgia rheumatica and giant cell arteritis. OARRR 2019;Volume 11:189–98.

73. Paskins Z, Whittle R, Sultan AA, Muller S, Blagojevic-Bucknall M, Helliwell T, et al. Risk of fracture among patients with polymyalgia rheumatica and giant cell arteritis: a population-based study. BMC Med 2018;16:4.

74. Da Silva JAP. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Annals of the Rheumatic Diseases 2006;65:285–93.

75. Lai LYH, Harris E, West RM, Mackie SL. Association between glucocorticoid therapy and incidence of diabetes mellitus in polymyalgia rheumatica and giant cell arteritis: a systematic review and meta-analysis. RMD Open 2018;4:e000521.

76. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis & Rheumatism 2006;55:420–6.

77. Mebrahtu TF, Morgan AW, West RM, Stewart PM, Pujades-Rodriguez M.

Oral glucocorticoids and incidence of hypertension in people with chronic inflammatory diseases: a population-based cohort study. CMAJ 2020;192:E295–301.

78. Albrecht K, Huscher D, Buttgereit F, Aringer M, Hoese G, Ochs W, et al. Long-term glucocorticoid treatment in patients with polymyalgia rheumatica, giant cell arteritis, or both diseases: results from a national rheumatology database. Rheumatol Int 2018;38:569–77.

79. Best JH, Kong AM, Unizony S, Tran O, Michalska M. Risk of Potential Glucocorticoid-Related Adverse Events in Patients with Giant Cell Arteritis: Results from a USA-Based Electronic Health Records Database. Rheumatol Ther 2019;6:599–610.

80. Christiansen CF, Christensen S, Mehnert F, Cummings SR, Chapurlat RD, Sørensen HT. Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study. Arch Intern Med 2009;169:1677–83.

81. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;114:735–40.

82. Mpofu S. Steroids, non-steroidal anti-inflammatory drugs, and sigmoid diverticular abscess perforation in rheumatic conditions. Annals of the Rheumatic Diseases 2004;63:588–90.

83. Wilson JC, Sarsour K, Collinson N, Tuckwell K, Musselman D, Klearman M, et al. Incidence of outcomes potentially associated with corticosteroid therapy in patients with giant cell arteritis. Semin Arthritis Rheum 2017;46:650–6.

84. Jamilloux Y, Liozon E, Pugnet G, Nadalon S, Heang Ly K, Dumonteil S, et al. Recovery of Adrenal Function after Long-Term Glucocorticoid Therapy for Giant Cell Arteritis: A Cohort Study. PLoS ONE 2013;8:e68713.

85. Wolkowitz OM, Burke H, Epel ES, Reus VI. Glucocorticoids: Mood,

Memory, and Mechanisms. Annals of the New York Academy of Sciences 2009;1179:19–40.

86. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The Neuropsychiatric Complications of Glucocorticoid Use: Steroid Psychosis Revisited. Psychosomatics 2012;53:103–15.

87. Gale S, Wilson JC, Chia J, Trinh H, Tuckwell K, Collinson N, et al. Risk Associated with Cumulative Oral Glucocorticoid Use in Patients with Giant Cell Arteritis in Real-World Databases from the USA and UK. Rheumatol Ther 2018;5:327–40.

88. Kermani TA, Warrington KJ, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, et al. Disease Relapses among Patients with Giant Cell Arteritis: A Prospective, Longitudinal Cohort Study. J Rheumatol 2015;42:1213–7.

89. Jobard S, Magnant J, Blasco H, Ferreira-Maldent N, Griffoul I, Diot E, et al. Quality of life of patients treated for giant cell arteritis: a case-control study. Clin Rheumatol 2017;36:2055–62.

90. Collison J. Tocilizumab improves quality of life in GCA. Nat Rev Rheumatol 2019;15:188–188.

91. Koster MJ, Matteson EL, Warrington KJ. Large-vessel giant cell arteritis: diagnosis, monitoring and management. Rheumatology (Oxford) 2018;57:ii32–42.

92. Brekke LK, Fevang BTS, Diamantopoulos AP, Assmus J, Esperø E, Gjesdal CG. Survival and death causes of patients with giant cell arteritis in Western Norway 1972–2012: a retrospective cohort study. Arthritis Res Ther 2019;21:154.

93. Garvey TD, Koster MJ, Crowson CS, Warrington KJ. Incidence, survival, and diagnostic trends in GCA across seven decades in a North American population-based cohort. Semin Arthritis Rheum 2021;51:1193–9.

94. Bas-Lando M, Breuer GS, Berkun Y, Mates M, Sonnenblick M, Nesher G.

The incidence of giant cell arteritis in Jerusalem over a 25-year period: annual and seasonal fluctuations. Clin Exp Rheumatol 2007;25:S15-17.

95. Ní Mhéalóid Á, Conway R, O'Neill L, Clyne B, Molloy E, Murphy CC. Vision-related and health-related quality of life in patients with giant cell arteritis. European Journal of Ophthalmology 2021;31:727–33.

96. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol 2017;13:476–84.

97. Jennings, G. H. Arteritis of the temporal vessels. Lancet 1938;231:424–8.

98. Bruce GM. Temporal arteritis as a cause of blindness; review of literature and report of a case. Trans Am Ophthalmol Soc 1949;47:300–16.

99. Birkhead NC, Wagener HP, Shick RM. Treatment of temporal arteritis with adrenal corticosteroids; results in fifty-five cases in which lesion was proved at biopsy. J Am Med Assoc 1957;163:821–7.

100. Singh AG, Kermani TA, Crowson CS, Weyand CM, Matteson EL, Warrington KJ. Visual manifestations in giant cell arteritis: trend over 5 decades in a population-based cohort. J Rheumatol 2015;42:309–15.

101. Liozon E, Herrmann F, Ly K, Robert PY, Loustaud V, Soria P, et al. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med 2001;111:211–7.

102. Salvarani C, Della Bella C, Cimino L, Macchioni P, Formisano D, Bajocchi G, et al. Risk factors for severe cranial ischaemic events in an Italian population-based cohort of patients with giant cell arteritis. Rheumatology (Oxford) 2009;48:250–3.

103. Nesher G, Berkun Y, Mates M, Baras M, Nesher R, Rubinow A, et al. Risk factors for cranial ischemic complications in giant cell arteritis. Medicine

(Baltimore) 2004;83:114–22.

104. Gonzalez-Gay MA, Piñeiro A, Gomez-Gigirey A, Garcia-Porrua C, Pego-Reigosa R, Dierssen-Sotos T, et al. Influence of traditional risk factors of atherosclerosis in the development of severe ischemic complications in giant cell arteritis. Medicine (Baltimore) 2004;83:342–7.

105. Nuenninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Mortality of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3532–7.

106. Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. Am J Med 1996;100:193–6.

107. Salvarani C, Crowson CS, O'Fallon WM, Hunder GG, Gabriel SE. Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. Arthritis Rheum 2004;51:264–8.

108. Goulabchand R, Qian AS, Nguyen NH, Singh AG, Roubille C, Parreau S, et al. Burden, Causes, and Outcomes of Hospitalization in Patients With Giant Cell Arteritis: A US National Cohort Study. Arthritis Care & Research 2023;75:1830–7.

109. Hino C, Edigin E, Aihie O, Odion J, Eseaton P, Okpujie V, et al. Longitudinal Trends of Hospitalizations for Giant Cell Arteritis: A 21-Year Longitudinal National Population-Based Study. Cureus [Internet] 2023 [cited 2024 Oct 18];Available from: https://www.cureus.com/articles/135710-longitudinal-trends-of-hospitalizations-for-giant-cell-arteritis-a-21-year-longitudinal-national-population-based-study

110. Michet Iii CJ, Achenbach SJ, Crowson CS, Matteson EL. Hospitalization rates and utilization among patients with giant cell arteritis: A population-based study from 1987 to 2012. Seminars in Arthritis and Rheumatism 2015;45:70–4.

111. Miloslavsky EM, Naden RP, Bijlsma JWJ, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76:543–6.

112. McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Glucocorticoid toxicity reduction with mepolizumab using the Glucocorticoid Toxicity Index. Eur Respir J 2022;59:2100160.

113. McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, et al. Quantification of Glucocorticoid-Associated Morbidity in Severe Asthma Using the Glucocorticoid Toxicity Index. The Journal of Allergy and Clinical Immunology: In Practice 2021;9:365-372.e5.

114. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med [Internet] 2021 [cited 2024 Oct 22];384. Available from: http://www.nejm.org/doi/10.1056/NEJMc2104672

115. Bakdash JZ, Marusich LR. Repeated Measures Correlation. Front. Psychol. 2017;8:456.

116. Corbera-Bellalta M, Planas-Rigol E, Lozano E, Terrades-García N, Alba MA, Prieto-González S, et al. Blocking interferon γ reduces expression of chemokines CXCL9, CXCL10 and CXCL11 and decreases macrophage infiltration in ex vivo cultured arteries from patients with giant cell arteritis. Ann Rheum Dis 2016;75:1177–86.

117. Bank U, Reinhold D, Kunz D, Schulz HU, Schneemilch Ch, Brandt W, et al. Effects of interleukin-6 (IL-6) and transforming growth factor-? (TGF-?) on neutrophil elastase release. Inflammation 1995;19:83–99.

118. Palamidas DA, Argyropoulou OD, Georgantzoglou N, Karatza E, Xingi E, Kapsogeorgou EK, et al. Neutrophil extracellular traps in giant cell arteritis biopsies: presentation, localization and co-expression with inflammatory cytokines. Rheumatology 2022;61:1639–44.

119. Samson M, Corbera-Bellalta M, Audia S, Planas-Rigol E, Martin L, Cid MC, et al. Recent advances in our understanding of giant cell arteritis pathogenesis. Autoimmunity Reviews 2017;16:833–44.

120. Maleszewski JJ, Younge BR, Fritzlen JT, Hunder GG, Goronzy JJ, Warrington KJ, et al. Clinical and pathological evolution of giant cell arteritis: a prospective study of follow-up temporal artery biopsies in 40 treated patients. Modern Pathology 2017;30:788–96.

121. Van Der Geest KSM, Abdulahad WH, Chalan P, Rutgers A, Horst G, Huitema MG, et al. Disturbed B Cell Homeostasis in Newly Diagnosed Giant Cell Arteritis and Polymyalgia Rheumatica. Arthritis & Rheumatology 2014;66:1927–38.

122. Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis. Arthritis & Rheumatism 2012;64:2001–11.

123. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and Th1 T-Cell Responses in Giant Cell Arteritis. Circulation 2010;121:906–15.

124. Weyand CM, Younge BR, Goronzy JJ. IFN-γ and IL-17: the two faces of T-cell pathology in giant cell arteritis. Current Opinion in Rheumatology 2011;23:43–9.

125. Weyand CM, Goronzy JJ. Medium- and Large-Vessel Vasculitis. N Engl J Med 2003;349:160–9.

126. Samson M, Audia S, Fraszczak J, Trad M, Ornetti P, Lakomy D, et al. Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatica pathogenesis. Arthritis & Rheumatism 2012;64:3788–98.

127. Miyabe C, Miyabe Y, Strle K, Kim ND, Stone JH, Luster AD, et al. An expanded population of pathogenic regulatory T cells in giant cell arteritis is abrogated by IL-6 blockade therapy. Ann Rheum Dis 2017;76:898–905.

128. Wang T, Sun X, Zhao J, Zhang J, Zhu H, Li C, et al. Regulatory T cells in rheumatoid arthritis showed increased plasticity toward Th17 but retained suppressive function in peripheral blood. Ann Rheum Dis 2015;74:1293–301.

129. Kleinewietfeld M, Hafler DA. The plasticity of human Treg and Th17 cells and its role in autoimmunity. Seminars in Immunology 2013;25:305–12.