What's New in Autoimmunity: New Autoantibodies, New Therapies, New Diseases

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The 9th International Congress on Autoimmunity was held in Nice, France, on 26–30 March 2014. Physicians and researchers from various medical specialties attended this meeting, which was an excellent occasion to exchange information on current research projects. This report summarizes some of the most impressive studies as well as new areas of research.

Noel R. Rose [1] charted the path of autoimmunity research which catapulted since the 1950s when he started to approach immunology. At that time he published an article in *JAMA* that changed the immunology world: he and his co-authors demolished the accepted medical dogma called "*horror autotoxicus*." According to this theory the body refuses to produce autoantibodies because they would cause damage; at that time all medical students learned this dictum. Rose demonstrated that antibodies versus thyroglobulin can be produced in vivo and can induce autoimmune thyroiditis. This was one of the most cited articles of that decade and changed the approach to autoimmunity. In the 1970s the contribution of genetics to the field of autoimmunity became clear through the definition of individual susceptibility linked to knowledge of major histocompatibility complex and related genes. In the last few decades autoimmunity has emerged more and more as an important component of human pathology, but we have still many miles to travel before we understand its fine mechanisms.

Every day new autoantibodies are studied. A group in Israel recently sought a correlation between anti-vitamin D antibodies and systemic sclerosis (SSc). Carmel et al. [2] studied immunoglobulin (Ig) G and M antibodies versus 25(OH)D and 1,25(OH)D in 54 SSc patients and 41 healthy controls. They selected this disease because SSc patients were known to have very low vitamin D levels, due to extensive skin involvement (preventing the activation), renal injury (interfering with the synthesis), as well as malabsorption in cases of advanced intestinal disease. Furthermore, patients with lower vitamin D levels seem to have more severe disease, especially regarding lung involvement. The authors found that anti-vitamin D antibodies were present in 87% of SSc patients and 42% of controls, and antibodies were mainly represented by IgM anti-25(OH)D with significant statistical difference between patients and controls. No correlation, however, was found between antibodies and other autoantibodies, disease severity, or target organ damage. Additional studies are needed but new ideas are emerging.

Many new autoantibodies have recently been identified in inflammatory myopathies. Selva-O'Callaghan et al. [3] summarized them to help clinicians in the difficult task of diagnosing and treating patients with these disorders. The classification currently in use is the one established in 1975 by Bohan and Peter, but in the last few years the newly described antibodies have been related to specific clinical phenotypes. Today, myositis-specific and myositis-associated antibodies need to be differentiated. For example, anti-transcriptional intermediary factor 1γ antibodies (anti-TIF1γ) seem to be a good marker of cancer-associated myositis; autoantibodies against melanoma differentiation-associated gene 5 (anti-MDA5) are associated with rapidly progressive interstitial lung disease, and anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase antibodies (anti-HMGCR) identify patients with statin-related myopathy. Recently, anti-cortactin antibodies were described and seem to be myositis-associated antibodies. The authors concluded that diagnosis and classification of myositis must include the identification of specific autoantibodies, and new criteria are hoped for.

Furthermore, some biomarkers, with a clear and well-known role in autoimmunity, were presented from a different standpoint: this is the case of interleukin-1 (IL-1). Cantarini and his group [4] likened IL-1 to "Ariadne's thread" through the labyrinth of autoinflammatory and autoimmune diseases. This cytokine, first discovered in the 1980s, plays a critical role in the pathways linking innate and adaptive immunity and could enable new therapeutic strategies. It is shown to be a strong mediator of inflammation and is involved in the pathogenesis of both autoinflammatory and autoimmune diseases; thus anti-IL1 agents might represent new weapons for treating these conditions.

Another potential forgotten therapeutic target is the complement system. The complement system is involved in the pathogenesis of several autoimmune diseases and was demonstrated to be directly involved in the development of inflammatory damage. Inhibition of the complement system in vasculitides has been investigated in only a few studies and only two complement modulators have been studied for humans (anti-C5 and anti-C1). This approach could represent a promising strategy in the near future [5]. In her article, Soriano [6] describes a currently ongoing phase 2 trial (CLEAR) of an

orally administered small molecule inhibitor of C5a receptor in patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). She also draws attention to B cells in AAV that have already been targeted with rituximab and could now be approached with other drugs, such as ofatunumab (an anti-CD20 with a greater complement-dependent cytotoxicity), epratuzumab (the anti-CD22 that could induce B cells anergy), and belimumab, which is currently under investigation for the prevention of small-medium vessel vasculitides.

B cells as a target in systemic lupus erythematosus were also discussed. Paran et al. [7] emphasize the contrast between the multiple roles of B cells implied in the pathogenesis of SLE and the less than impressive results obtained until now with B cell-targeting treatments.

Belimumab has been tested in two large clinical trials with sufficient statistical power to demonstrate only a modest beneficial effect, but its steroid-sparing effect could significantly reduce the related organ damage. The use of a new composite endpoint, the SLE Responder Index (SRI), perfectly captures this aspect. Another discussed B cell drug is rituximab, which showed beneficial effects in open-label uncontrolled studies in more than 400 patients worldwide. Nevertheless, it failed the primary endpoints in the randomized clinical trials (RCTs) that aimed to demonstrate its superiority over classic immunosuppressants alone (high dose corticosteroids, mycophenolate mofetil). A possible explanation for this discrepancy could be the different patients selected: the typical patient in open-label studies had life-threatening manifestations refractory to the conventional therapy, while this type of subject was excluded from RCTs. Moreover, RCT patients also received conventional therapy, possibly masking RTX's beneficial effects.

However, biologic drugs can act as a double-edge sword: in recent years increasing attention has been paid to the unexpected negative actions on the immune system. For example, anti-tumor necrosis factor (TNF), which is indicated for the treatment of psoriasis, could also induce it. Watad et al. [8] describe a severe clinical presentation of TNF-induced pneumonia. In the BIOGEAS registry 122 patients affected by autoimmune diseases with an interstitial lung disease (ILD) induced or exacerbated by biologic drugs have been collected. In particular, 89% of them were affected by rheumatoid arthritis (RA) and in virtually all cases the drug in question was an anti-TNF. Since ILD is frequent among RA extra-articular manifestations, a clinical-therapeutic issue could be whether to introduce an anti-TNF in a patient who has already been diagnosed with ILD. Does anti-TNF really increase the risk of exacerbation? Anti-TNF-induced pneumonia also offers a differential diagnostic challenge: how to distinguish an infectious pneumonia, more frequent in these patients, from a drug-induced one? Drug-induced pneumonia, although rare, should be considered in these subjects.

Moreover, it is now well known that biologic drugs can also induce the production of autoantibodies (antinuclear antibody, anti-double strand DNA), even if it is not clear why anti-TNF could decrease titers of rheumatoid factor and anti-cyclic citrullinated peptides antibodies (anti-CCP), while inducing other autoantibodies. Fortunately, most patients never develop related clinical manifestations. Roginić and co-authors [9] present the case of etanercept-induced SLE and suggest that targeting TNF could enhance some crucial steps of SLE pathogenesis; for example, reducing the clearance of apoptotic material or increasing the secretion of interferon-alpha through the induction of a cytokine imbalance. However, treatment with anti-TNF did have some positive unexpected effects. Kovacs et al. [10] report successful etanercept therapy in a case of primary cirrhosis associated with RA: a considerable reduction in both arthritis activity and cholestatic markers was noted. In the medical literature, two other cases of this association treated with biologic drugs were described: one successful with etanercept and the other unsuccessful with infliximab for both articular and liver disease [10,11]. Selmi et al. [11] also underline that the only definite proof of the role of TNF in the pathogenesis of primary biliary cirrhosis is its reduction after treatment with ursodeoxycholic acid, the only therapy approved until now.

Interestingly, some challenging clinical cases were also discussed at this Congress. Sharabi and team [12] described the case of a woman with systemic sclerosis sine scleroderma and severe digital ulcers as a feature of paraneoplastic syndrome. They successfully treated the patient with bosentan (125 mg twice a day); the response was immediate and no recurrence of ulcers was observed during 2 years of follow-up. One year after presentation the patient was diagnosed with lung cancer. Systemic sclerosis sine scleroderma could be the expression of an occult cancer that becomes clinically evident later; however, the authors concluded that skin lesions seem to be well controlled with conventional therapy.

Watad and colleagues [13] consider the case of polymyositis (PM) following lengthy treatment with statins; only two other similar cases were previously described. Muscular symptoms in patients with long-term statin treatment could be the first symptom of polymyositis; this finding should encourage the physician to perform antinuclear antibodies screening especially in a case of proximal muscular weakness and increased muscle enzyme levels. Bohan and Peter's diagnostic criteria for PM must always be considered if there is any suspicion, especially because, in rare cases, statins may trigger myopathies that do not resolve despite discontinuing therapy and require immunosuppressive treatment.

Another clinical dilemma is livedo reticularis. Sangle and D'Cruz [14] present a detailed review of its history, exploring different clinical aspects, pathophysiology, differential diagnosis and treatment. The authors concluded that livedo is a common cutaneous manifestation of some immunologic diseases, especially antiphospholipid syndrome. It may be a prognostic marker of a more severe disease, and it seems to be associ-

ated with thrombosis and pregnancy morbidity, irrespective of the presence of antiphospholipid antibodies**;** recent results also suggest the possibility of an association with accelerated atherosclerosis. Therefore, livedo reticularis could be a clinical marker of the so-called seronegative antiphospholipid syndrome, although the exact relationship remains to be explored.

New autoimmune disorders have recently been investigated, including the so-called ASIA (autoimmune syndromes induced by adjuvants). Austin and collaborators [15] described the interesting case of a man who developed transverse myelitis 2 months after immunization with influenza A (H1N1). Serious adverse reactions are relatively rare post-vaccination, but there are some evidences of a link between vaccine adjuvants and the development of autoimmune phenomenon, and case reports that describe similar episodes have been published.

On the other hand Katz-Agranov et al. [16] described a case of two well-known immunological disorders, Takayasu's arteritis and giant cell arteritis, unusually associated. Is this really infrequent? Or are we under-diagnosing large vessel involvement in giant cell arteritis? The two diseases occur in patients of different ages and display a rather different course; however, classification criteria were drawn without the aid of radiological advances in vascular diagnosis. This case report supports the already formulated hypotheses that large vessel vasculitis could exist on a continuum within the same disease in which clinical expression is influenced by different factors.

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