Special Article

Safety of treatments for inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

Livia Biancone [a,*,1], Vito Annese [c], Sandro Ardizzone [d], Alessandro Armuzzi [e], Emma Calabrese [a], Flavio Caprioli [f], Fabiana Castiglione [g], Michele Comberlato [h], Mario Cottone [i], Silvio Danese [j], Marco Daperno [k], Renata D'Incà [l], Giuseppe Frieri [m], Walter Fries [n], Paolo Gionchetti [o], Anna Kohn [p], Giovanni Latella [m], Monica Milla [c], Ambrogio Orlando [i], Claudio Papi [q], Carmelina Petruzziello [a], Gabriele Riegler [r], Fernando Rizzello [o], Simone Saibeni [s], Maria Lia Scribano [p], Maurizio Vecchi [t], Piero Vernia [u], Gianmichele Meucci [b,1]

[a] Gastroenterology Unit, University of Rome "Tor Vergata", Department of Systems Medicine, Rome, Italy
[b] San Giuseppe Hospital, Gastroenterology, Milan, Italy
[c] AOU Careggi, Gastroenterology, Florence, Italy
[d] Gastrointestinal Unit, ASST Fatebenefratelli Sacco – University of Milan, Milan, Italy
[e] IBD Unit, Presidio Columbus, Fondazione Policlinico Gemelli Universita' Cattolica, Rome, Italy
[f] Department of Pathophysiology and Transplantation, University of Milan and Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda,Ospedale Policlinico di Milano, Milan, Italy
[g] Gastroenterology Unit, University 'Federico II', Naples, Italy
[h] Department of Gastroenterology and Digestive Endoscopy, Central Hospital, Bolzano, Italy
[i] Division of Internal Medicine 2, IBD Unit, Hospital "Riuniti Villa Sofia-Cervello", Palermo, Italy
[j] Humanitas Research Hospital and Humanitas University, Rozzano (Milan), Italy
[k] Hospital "Ordine Mauriziano di Torino", Turin, Italy
[l] Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Italy
[m] University of L'Aquila, Gastroenterology Unit, L'Aquila, Italy
[n] Department of Clinical and Experimental Medicine, Clinical Unit for Chronic Bowel Disorders, University of Messina, Messina, Italy
[o] IBD Unit, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
[p] San Camillo-Forlanini Hospital, IBD Unit, Rome, Italy
[q] IBD Unit, San Filippo Neri Hospital, Rome, Italy
[r] U.O. of Gastroenterology C.S. - University della Campania "Luigi Vanvitelli", Naples, Italy
[s] Gastroenterology Unit, Rho Hospital, ASST Rhodense, Rho, Italy
[t] Gastroenterology and Gastrointestinal Endoscopy Unit, IRCCS Policlinico San Donato and University of Milan, San Donato Milanese, Milan, Italy
[u] Gastroenterology Unit, Sapienza, University of Rome, Rome, Italy

ARTICLE INFO

ABSTRACT

Inflammatory bowel diseases are chronic conditions of unknown etiology, showing a growing incidence and prevalence in several countries, including Italy. Although the etiology of Crohn's disease and ulcerative colitis is unknown, due to the current knowledge regarding their pathogenesis, effective treatment strategies have been developed. Several guidelines are available regarding the efficacy and safety of available drug treatments for inflammatory bowel diseases. Nevertheless, national guidelines provide additional information adapted to local feasibility, costs and legal issues related to the use of the same drugs. These observations prompted the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) to establish Italian guidelines on the safety of currently available treatments for Crohn's disease and ulcerative colitis. These guidelines discuss the use of aminosalicylates, systemic and low

* Corresponding author at: GI Unit, Department of Systems Medicine, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy.
E-mail address: biancone@med.uniroma2.it (L. Biancone).
[1] These authors contributed equally to this work.

Medical treatments
Safety

bioavailability corticosteroids, antibiotics (metronidazole, ciprofloxacin, rifaximin), thiopurines, methotrexate, cyclosporine A, TNFα antagonists, vedolizumab, and combination therapies. These guidelines are based on current knowledge derived from evidence-based medicine coupled with clinical experience of a national working group.

1. Introduction

Several treatments are currently available for treating inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC). These treatments are primarily aminosalicylates [1–9], systemic corticosteroids [1–7], topical corticosteroids (budesonide; beclomethasone dipropionate, BDP) [10–12], and antibiotics (ciprofloxacin, metronidazole, rifaximin) [13–15]. Immunomodulators, including thiopurines (azathioprine, 6-mercaptopurine, 6-MP) [1,16–20], methotrexate [21] and cyclosporine A (CsA) [22,23], also show efficacy in IBD [1,16–23]. Since 1995 [24], a marked efficacy has also been shown for biologic therapies, including monoclonal antibodies against tumor necrosis factor-α (anti-TNFα) (infliximab, adalimumab, golimumab, infliximab biosimilars) [25–33] and, more recently, against integrins (vedolizumab, natalizumab) [1,2,34]. Combinations of these therapies are often used.

The European Crohn's and Colitis Organization (ECCO) has published guidelines for the management of IBD [6,7]. Nevertheless, national guidelines are also valuable because they take into consideration the local availability, feasibility and costs of both treatments and diagnostic approaches. National guidelines are also helpful because economic and legal issues differ between countries [35]. The Italian Society of Gastroenterology and the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) have already established Italian guidelines on the use of biologics in IBD [36]. However, guidelines on the safety of treatments for adult IBD patients are not yet available in Italy.

The IG-IBD therefore decided to prepare the present guidelines on the safety of IBD treatments available in Italy. The safety of the following treatments was considered: aminosalicylates, sulfasalazine, systemic and locally released corticosteroids, ciprofloxacin, metronidazole, rifaximin, thiopurines, methotrexate, CsA, TNFα antagonists, and vedolizumab.

For this purpose, 50 gastroenterologists, all belonging to IG-IBD and working at one of 28 IBD units at Italian Universities and Hospitals, agreed to participate in writing these national guidelines. The working group included two coordinators (from two institutes), 26 writers (from 20 institutes), and 22 discussants (from 20 institutes). Additionally, one expert in infectious diseases, one oncologist and one general practitioner were involved in drawing up the consensus and in making the online evaluations, for a multidisciplinary approach. Overall, 53 panelists discussed and approved the text and the statements. Statements elaboration was followed by consensus conferences in order to discuss the preliminary statements. Agreement (>85%) was reached after 5 online votes. Each statement was discussed by the 53 panelists, who met in Rimini (Italy) on November 11th, 2014, for a general consensus meeting (participants 43/53 panelists). Statements were further discussed and voted during 5 online voting procedures. Dates of these 5 sequential online voting procedures were: October 5th–30th, 2014 (participants 49/53 panelists); November 26th–December 12th, 2014 (participants: 52/53); April 12th–29th, 2015 (participants: 52/53); July 11th–28th, 2015 (participants: 51/53), September 11th–October 17th, 2015 (participants: 52/53). In order to formulate recommendations, each expert performed a literature search using the following key words: CD, UC, IBD, safety, treatments, aminosalicylates,

sulfasalazine, systemic and low bioavailability corticosteroids, ciprofloxacin, metronidazole, rifaximin, thiopurines, azathioprine, 6-MP, methotrexate, CsA, TNFα-antagonists, infliximab, adalimumab, golimumab, infliximab-biosimilars, vedolizumab. For THE literature searches, PubMed, Embase and the Cochrane database were used, including articles published until September 2016. The Oxford methodology was used to establish levels of evidence (Table 1) [37].

2. Aminosalicylates

Sulfasalazine [38] has been the mainstay of UC therapy for a long time. However, the frequent occurrence of adverse events (AEs) limited its use. In the 1970s, it was discovered that sulfasalazine is broken down in the ileocolonic tract to 5-aminosalicylic acid (5-ASA), the therapeutic moiety, and sulfapyridine, which serves as carrier [39]. As the AEs appeared to be related to sulfapyridine, new ways to deliver 5-ASA were developed and, currently, oral mesalazine is available in several formulations with different mechanisms of release; all show a very low systemic absorption.

Two systematic reviews that compared different 5-ASA preparations (olsalazine, mesalazine, balsalazide) to placebo reported a comparable incidence of AEs leading or not to withdrawal [40,41]. The proportions of treated patients experiencing ≥1 AE and withdrawing due to AEs were higher among those using sulfasalazine than 5-ASA (29% vs. 15% and 13% vs. 5% respectively). Olsalazine caused dose-dependent secretory diarrhea more frequently than mesalazine and balsalazide did (10% vs. 2% and 5%, respectively) [40]. Other frequent AEs caused by olsalazine, mesalazine and balsalazide are nausea/vomiting (3%–8%), headache (4%–5%), abdominal pain/dyspepsia (4%–6%), rash (2%–4%), fever (3%–4%), fatigue/weakness (2%–4%), and arthralgia/myalgia (1%–3%) [40]. Mesalazine also causes hepatic biochemical abnormalities in 2% of cases and pruritus in 1%.

A comparison between various 5-ASA formulations (balsalazide, pentasa, olsalazine, 5-ASA micropellets) and comparator 5-ASA formulations showed the same incidence of AEs (46% and 46%, respectively) [40]. A review of all data from a Cochrane analysis confirmed this equivalence [42]. Kamm et al. [43] reported no difference between mesalazine multimatrix system (MMX), conventional 5-ASA formulations and placebo in terms of AEs, with no dose-related effects.

2.1. Side effects

Not all AEs can be classified as either dose-dependent or idiosyncratic; some may be associated with both mechanisms. In 1995, alopecia was reported as a dose-dependent side effect of 5-ASA in 1%–2% of patients [44]. Idiosyncratic reactions using 5-ASA include skin rashes, fever, agranulocytosis, focal hepatitis, polyarteritis, and neurotoxicity [45–50]. Data regarding pancreatitis and 5-ASA are conflicting [51–54], as there have been reports of both no increased risk [55] and a 4- to 9-fold increased risk [56,57]. Many of the AEs associated with sulfasalazine have been ascribed to sulfapyridine [45,53,58,59]. This observation is supported by the correlations between AEs and both serum sulfapyridine levels and slow sulfadimidine acetylator phenotype [60]. Initially, hematological side effects were ascribed to the sulfapyridine moiety of sulfasalazine.

Table 1
Oxford Centre for evidence-based medicine 2011 levels of evidence.

Question	Level 1	Level 2	Level 3	Level 4	Level 5
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances	Local non-random sample	Case-series	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards	Case-control studies, or "poor" or non-independent reference standard	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial	Case-series or case-control studies, or poor quality prognostic cohort study	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study	Case-series, case-control studies, or historically controlled studies	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm (for long-term harms the duration of follow-up must be sufficient)	Case-series, case-control, or historically controlled studies	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study		
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study	Case-series, case-control, or historically controlled studies	Mechanism-based reasoning

Modified from Reference [37].

However, these AEs have also been observed with mesalazine, with reports of thrombocytopenia [61,62], leukopenia [62–64] and aplastic anemia [65,66]. In most of these cases, the AEs are both idiosyncratic and dose-independent [67].

Mesalazine-induced pericarditis has low incidence and mostly occurs during the first weeks of treatment [68]. This AE is considered an acute hypersensitivity reaction against 5-ASA [68–70]. Overall, long-term 5-ASA treatment is widely considered safe. Severe AEs are rare [6,7,71,72].

2.1.1. Renal toxicity

The most controversial mesalazine-related AE is probably renal toxicity [73,74]. Elevated urinary levels of markers of renal tubular damage were found in 20%–30% of IBD patients [75]. The damaged renal function is believed to be an extraintestinal manifestation of IBD or the result of an inflammatory process [75,76]. Thus, also IBD patients not using 5-ASA may be at risk of renal disease. European and American guidelines therefore recommend regular renal function monitoring [77,78].

Several cases of 5-ASA-induced interstitial nephritis have been reported [79–83]. Because this complication presents with nonspecific symptoms and signs, detection may be delayed for months. The incidence of 5-ASA-related nephrotoxicity is <0.5% [79,83]. About 50% of cases of 5-ASA-induced interstitial nephritis develop in less than 1 year [80]. Therefore, serum creatinine monitoring is recommended at 3- to 6-month intervals during the first year and annually thereafter [7,77]. There is no evidence that more frequent testing improves patient outcome. Mesalazine should be withdrawn when renal impairment occurs. If renal function does not improve, renal biopsy should be considered [83].

2.2. Pregnancy

The classification of each treatment used in IBD, according to the pregnancy categories of the US Food and Drug Administration (FDA), is given in Table 2 [84]. Mesalazine, sulfasalazine and balsalazide are category B drugs for pregnancy, whereas olsalazine is included in category C. Mesalazine use has not been associated with an increased risk of complicated pregnancy in IBD patients. However, there have been reports of mesalazine-related preterm deliveries and low birth weight [85–93]. Continuing mesalazine throughout pregnancy is strongly recommended, since IBD reactivation during pregnancy is more harmful than treatment [94].

2.3. Surgery

No studies have specifically addressed the safety of mesalazine in patients undergoing surgery. There is no evidence that mesalazine is associated with surgical complications.

Statement 1
The safety of 5-ASA formulations, for both oral and rectal use, is established at all approved doses [EL1]. Sulfasalazine may cause some AEs due to the systemic absorption of sulfapyridine [EL5].

Statement 2
Renal function should be monitored at least yearly during treatment [EL3]. In patients with chronic renal failure, renal function should be monitored more closely [EL3].

Statement 3
Mesalazine appears to be safe during pregnancy [EL1] and lactation [EL5]. In case of treatment with salazopyrin, folate supplementation is recommended [EL5].

3. Systemic corticosteroids

Systematically acting corticosteroids significantly reduce mortality related to IBD activity, as almost 80% of patients with active

Table 2
The FDA pregnancy category chart.

Category A	Adequate research has been done with the conclusion that drugs in this category are not likely to cause any harm to the fetus in the first trimester as well as later in pregnancy.
Category B	Studies carried out on animals have shown no adverse effects on the fetus; however, there is a lack of controlled studies on human pregnancy.
Category C	Animal studies have shown evidence of harmful effects on the fetus; however, no controlled study has been done on a human pregnancy. The medicines may be prescribed in cases where the potential benefits outweigh the possible adverse effects.
Category D	Studies done on human pregnancy have shown positive risks to the fetus. However, doctors might prescribe them in certain cases where the potential benefits outweigh the risks.
Category X	Both human and animal studies have shown positive risks to the fetus, with the adverse effects extending to serious birth defects, miscarriage and fetal death. The possible risks of using these medicines outweigh any potential benefits.

Modified from Reference [84].

disease have a positive treatment response [6,7]. Nonetheless, these drugs cause several side effects that limit their recurrent or long-term use.

3.1. Hemorrhagic risk

The risk of peptic ulcer and gastroduodenal bleeding is irrelevant. Proton pump inhibitors are therefore not needed when using corticosteroids. This point has been made by the Italian drug agency (Agenzia Italiana del Farmaco, AIFA) [95].

3.2. Diabetes, hypertension and metabolic disorders

Corticosteroids can increase blood glucose and compromise glycometabolic balance in non-diabetic individuals. Long-term use (6–18 months) of these drugs can therefore cause weight gain, cushingoid habitus and reduced muscle mass [96–98]. Arterial hypertension is thought to develop in 20% of patients using corticosteroids [96,97]. Long-term corticosteroid use also modifies hypophysis–adrenal gland feedback, and may therefore reduce endogenous synthesis of glucocorticoids [6,7]. An abrupt discontinuation of corticosteroids may cause temporary adrenal failure [6,7]. Therefore, tapering is recommended in order to avoid adrenal failure [6,7,99]. Other symptoms include fatigue, malaise, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful and itching dermal lumps, and weight gain.

3.3. Surgical complications

Corticosteroids mainly induce infections related to Candida spp. [6,7,100]. No specific infection appears to be associated with immunomodulators [101]. When taken before surgery, corticosteroids (particularly at higher doses) increase the risk of infectious and non-infectious complications in patients with IBD [102–104].

3.4. Osteopenia and osteoporosis

Increased risks of bone mass reduction and bone fracture in corticosteroid-treated patients have been shown in a meta-analysis [105]. These risks were significant for patients taking corticosteroids >5 mg/day for 3–6 months, and decreased after withdrawal. Chronic corticosteroid use increases the risk of osteoporotic fractures independently of bone mineral density [106]. In children, corticosteroids inhibit linear growth, delay skeletal maturation, and reduce final height and bone mineralization [6,7]. Osteonecrosis of the femoral head is an uncommon albeit worrisome complication [107].

3.5. Pregnancy, breastfeeding, fertility

Corticosteroids do not interfere with pregnancy, breastfeeding or fertility in females. Sperm quality is not altered by steroids

[108,109]. The FDA classifies systemic corticosteroids in pregnancy category C (Table 2).

3.6. Ocular manifestations

The most frequent corticosteroid-induced ocular AEs are posterior subcapsular cataract and glaucoma [110]. Corticosteroid-induced cataract cannot be prevented [6,7,111]. In patients with uncontrolled glaucoma, corticosteroids must be withdrawn; intra-ocular pressure will normalize within 2–4 weeks [6,7,111]. The frequency of these AEs ranges from 10% to 15%, depending on dosage, duration and individual predisposition [6,7,111].

3.7. Psychological and behavioral disturbances

Psychiatric disorders (affective, behavioral, cognitive) are not observed in IBD patients taking low corticosteroid doses (<20 mg/day), while these AEs may occur in those taking higher doses (1.3% at 40 mg/day; 5% at 41–80 mg/day) [98].

3.8. Mortality

In a multivariate logistic regression analysis of the TREAT registry, an increased mortality risk in CD (OR 2.10) was associated with the use of prednisone [112].

Statement 4
In short-term therapy, steroid side effects are usually limited [EL3]. Treatment with proton pump inhibitors is generally not recommended [EL1].

Statement 5
The most frequent side effects associated with prolonged use of steroids are hypertension, diabetes, osteopenia, osteoporosis, cataract and glaucoma [EL1]. Patients should be checked regularly for blood and ocular pressures, plasma glucose levels, glucose tolerance, and bone mineral density [EL5]. The use of steroids for more than 3 months should be avoided [EL3].

Statement 6
Elective surgery should be avoided in patients taking prednisone ≥20 mg/day (or equivalent) in order to avoid post-surgical complications [EL3].

Statement 7
The short-term use of steroids does not influence fertility or pregnancy; their use during pregnancy is safe [EL1].

4. Low bioavailability corticosteroids

Budesonide and beclomethasone dipropionate (BDP) have high topical glucocorticoid activity. After mucosal absorption, these drugs enter the bloodstream and are inactivated by the liver, with limited residual systemic glucocorticoid activity. However, because only 80%–90% of circulating molecules are inactivated, these drugs can cause some AEs [113].

Budesonide (9 mg/day) is an established treatment for mild-moderate ileocecal CD [12]. BDP (5–10 mg/day) [11] and, more recently, budesonide coated in MMx system, showed efficacy in mild-moderate UC [114].

4.1. Short-term side effects

Several randomized controlled trials (RCTs) compared budesonide with placebo [115,116], 5-ASA [117,118] or systemic corticosteroids [119–123] in patients with active CD. In active UC, budesonide has been compared with placebo [114,124,125], 5-ASA [124,126] and systemic corticosteroids [127].

In one double-blind RCT, the rates of AEs and corticosteroid-related side effects were similar between budesonide, placebo and 5-ASA, with the exception of moon face [115]. This favorable safety profile was also observed for budesonide MMx [128]. When compared with systemic corticosteroids, budesonide induced a similar rate of total AEs, but a lower rate of corticosteroids-related AEs [129]. In the few RCTs that compared BDP with placebo, AEs were infrequent and generally not serious [12,130,131]. When BDP was compared with systemic corticosteroids, the rate of AEs was comparable [122,131].

4.2. Long-term side effects

Budesonide has been compared with placebo, in patients with CD, for maintaining remission in CD [11,132–136] and for preventing post-operative recurrence of CD [137,138]. In these studies, the rates of side effects were comparable between the two treatment groups, with the exception of moon face [133] and bruising [135]. Budesonide caused fewer corticosteroid-related AEs than prednisolone [139]. Other AEs from budesonide are acne, moon face, hirsutism, mood swings, insomnia, weight gain, striae, and hair loss. A double-blind, placebo-controlled RCT reported comparable frequencies of AEs in CD patients treated with BDP (51.4%) or with placebo (58.3%) [140].

4.3. Adrenal suppression/withdrawal symptoms

Low bioavailability corticosteroids are more likely to cause a significant reduction in plasma cortisol levels than 5-ASA or placebo [113–116,122,123,130–132,136]. Budesonide [119,121] and BDP [131] induce a comparable reduction in plasma cortisol levels, which nonetheless is less clinically relevant than the reduction induced by systemic corticosteroids. Impaired adrenal function (seen as altered results on adrenocorticoid stimulation tests) develops in a higher proportion of IBD patients using budesonide than 5-ASA or placebo (in both the short and long terms, even at a low dose such as 3 mg/day) [135,139].

4.4. Bone damage

Short-term budesonide use does not appear to impair osteoblast activity in CD [141]. In a randomized 2-year study [138], bone mineral density was better preserved in patients taking budesonide than prednisone in mild-moderate corticosteroid-naïve CD, but not in patients with steroid dependence or previous exposure to corticosteroids. In a 2-year prospective study [142], budesonide was associated with bone loss, without advantage over low-dose prednisone.

4.5. Other side effects

In a pooled safety analysis of five double-blind, placebo-controlled RCTs at 1 year [143], cutaneous glucocorticoid signs were more frequent in patients who were using budesonide

(p = 0.0036). Clinically relevant AEs were rare and similar between groups.

4.6. Surgery

Budesonide and BDP are both considered pregnancy category C drugs (Table 2). Systemic corticosteroids have been suggested for patients using budesonide or BDP requiring emergency surgery [115]. The risk of surgical complications in IBD patients treated with budesonide or BDP is undefined.

4.7. Pregnancy and breastfeeding

A few studies have reported the safety of oral budesonide and BDP in pregnancy or breastfeeding. No maternal or fetal AEs were reported for eight pregnant women taking budesonide (6–9 mg/day) for IBD [144]. In asthmatic pregnant women, use of inhaled budesonide was not associated with an increased risk of congenital malformations, cardiovascular defects, decreased gestational age, or reduced birth weight/length [145]. According to a systematic review, only one of nine included studies of BDP for asthma in pregnant women without IBD reported an increased risk of congenital abnormalities [146]. No similar data are available regarding patients with IBD. Although budesonide and BDP are secreted in breast milk, the levels of these drugs in breast milk and in lactating infants' plasma are low [147,148]. Therefore, these drugs are considered compatible with breastfeeding [147,148]. However, we suggest that the decision to prescribe low-bioavailability corticosteroids to nursing women be made on a case-by-case basis.

Statement 8

In the short term, BDP and budesonide appear to be safer than systemic steroids [EL1].

Statement 9

In the long term, budesonide treatment leads to adrenal suppression, has a negative effect on bone mineral density, and may cause cutaneous glucocorticoid signs [EL1]. Moreover, considering its lack of effectiveness in maintenance therapy, its use should not last for more than 3 months following induction of remission [EL5].

Statement 10

The use of budesonide and BDP during lactation should be evaluated case by case [EL5].

5. Antibiotics

In IBD, antibiotics are appropriate for treating perianal CD, septic complications, bacterial overgrowth, and active pouchitis [6,7,149,150]. The main antibiotics used in IBD are ciprofloxacin, metronidazole and rifaximin.

5.1. Ciprofloxacin

Ciprofloxacin is safe and well tolerated [151]. Most AEs due to ciprofloxacin are mild and self-limiting, and rarely require the drug's discontinuation. Gastrointestinal toxicity (nausea, dyspepsia, vomiting, abdominal pain, constipation, diarrhea) occurs in ≤20% of patients [151,152]. Ciprofloxacin may cause *C. difficile* infection, inducing IBD relapse [153]. Mild, transient elevations of transaminases and alkaline phosphatase are occasionally observed [154]. Rarely, serious acute liver injury, mainly related to idiosyncratic hypersensitivity, has been reported [154]. Pre-existing liver disease is a risk factor for a poorer outcome [154]. Hypo- or hyperglycemia may be observed [152].

During ciprofloxacin treatment, patients may experience neurological and psychiatric events such as headache, insomnia,

somnolence, confusion state, acute psychosis, delirium, convulsions and dizziness [152,155]. Ciprofloxacin should be used with caution in patients with a history of seizures.

Ciprofloxacin can cause arthropathy, primarily in weight-bearing joints and especially in pediatric patients [156,157]. Tendinitis and tendon rupture, primarily affecting the Achilles tendon, may occur. This event is rare, with an excess risk of 3.2 cases/1000 patient-years [158]. Corticosteroid use, old age and intense physical activity enhance this risk [159]. As QT interval prolongation has been observed in quinolone treatment [160], ciprofloxacin should be avoided in patients with this abnormality or other risk factors for tachyarrhythmia. Finally, a common complication of ciprofloxacin use is mild-to-severe phototoxicity [151,152].

5.2. Metronidazole

The incidence of AEs in patients using metronidazole varies according to the dose and duration. Long-term use (3 months) at high dose (20 mg/kg day) induced AEs in 38% of patients [161]. AEs from metronidazole include metallic taste, nausea, anorexia and diarrhea. Hypersensitivity reactions (e.g. fever, rash, itch, flush, vomiting, abdominal cramp, headache, stomatitis, glossitis, dry mouth) may occur. These symptoms usually resolve with dose reduction or cessation. Rarely, a disulfiram-like reaction after alcohol consumption may develop, although the role of this interaction is debated [162]. Dark-colored urine and transient reversible neutropenia may occur in patients taking high-dose metronidazole [163]. It is useful to closely monitor leukocyte levels, in patients assuming metronidazole combined with immunosuppressives.

AEs from metronidazole involving the central nervous system include dizziness, encephalopathy, seizure, cerebellar ataxia and, more frequently, peripheral neuropathy [164] leading to paresthesias or subclinical delayed nerve conduction. These neurological AEs occur in up to 85% of patients after long-term treatment with high doses (20 mg/kg day) [161,165,166]. These symptoms and structural lesions usually resolve after drug withdrawal, although the peripheral neuropathy may take several months to resolve; if treatment is continued, the symptoms may become irreversible.

5.3. Rifaximin

Rifaximin has an excellent safety profile, with AEs occurring in ≤2% of patients [167,168]. Common AEs are flatulence, abdominal pain, nausea and vomiting. Increased serum potassium and sodium levels, although within the normal range, may occur. Long-term treatment with high doses of rifaximin has been associated with urticarial skin reactions [167,168].

5.4. Use of antibiotics by pregnant or lactating women

Two studies of pregnant women taking ciprofloxacin did not observe any risk of spontaneous abortion or congenital malformation associated with this drug [169,170]. Overall, ciprofloxacin is thought to present minimal risk to pregnant women. However, the ECCO guidelines [171] suggest avoiding ciprofloxacin during the first trimester, while for the FDA ciprofloxacin is included in pregnancy category C [172]. Because ciprofloxacin is excreted in breast milk, ECCO recommends that it not be taken by lactating women [171].

Metronidazole use in pregnant women has been associated with an increased risk of infant cleft lip, with or without cleft palate [173,176], although two meta-analyses found no relationship between metronidazole exposure during pregnancy and birth defects [174,175]. Metronidazole is considered a low-risk drug for pregnant women (FDA pregnancy category B). However, its use

during the first trimester is not recommended [171,172]. Metronidazole is secreted in breast milk [177] and, therefore, breastfeeding should be avoided during treatment.

Finally there are no relevant data regarding teratogenicity of rifaximin in humans (FDA category C) [172]. The American Gastroenterological Association suggests that rifaximin is probably compatible with breastfeeding, but data are lacking [172].

Statement 11
Gastrointestinal intolerance is the most common side effect of ciprofloxacin, observed in up to 20% of patients [EL2]. Ciprofloxacin can cause Clostridium difficile infection [EL4]. Concomitant use of steroids and ciprofloxacin, especially in the elderly, should be avoided due to the risk of tendinitis and tendon rupture [EL4].

Statement 12
Usual side effects of metronidazole include metallic taste, nausea, anorexia and diarrhea, which usually resolve with dose reduction or drug discontinuation [EL2]. Peripheral neuropathy is reported in up to 85% of patients treated at high doses (20 mg/kg day) for long time [EL3]. Neuropathy may be irreversible if treatment continues [EL4].

Statement 13
Side effects of rifaximin are reported in less than 2% of patients, and mostly concern the gastrointestinal tract [EL3].

Statement 14
Ciprofloxacin and metronidazole should be avoided during pregnancy, especially in the first trimester [EL5]. However, short-term courses of metronidazole are possible during the second and third trimesters [EL5]. Rifaximin should be avoided during pregnancy [EL5]. Ciprofloxacin and metronidazole should be avoided during lactation [EL5], while rifaximin is probably safe [EL5].

6. Thiopurines

Thiopurines, including 6-mercaptopurine and its prodrug azathioprine, induce AEs in more than 30% of IBD patients. Drug discontinuation is required in 20%–40% of these cases [178–181]. The estimated number needed to harm (NNH) is 14 [182]. Thiopurine AEs may be dose-unrelated (idiosyncratic or allergic, probably immune-mediated) or dose-related.

Idiosyncratic AEs generally occur early. The most common forms of these AEs are nausea, vomiting, pancreatitis, cutaneous eruption and hepatitis, most often associated with systemic symptoms (e.g. malaise, fever, and articular or muscular pain). Pancreatitis is usually mild; it occurs in 1%–4% of patients, mainly females, within 1 month, although a later onset is possible [178–181]. Rechallenge with any thiopurine almost invariably leads to recurrent pancreatitis. Cutaneous eruptions are often under-recognized because they can mimic infections or the exacerbation of an underlying cutaneous disease. The most common manifestation of hypersensitivity is neutrophilic dermatosis, which in some cases meets the criteria of drug-induced Sweet's syndrome [183].

Dose-related AEs, including myelotoxicity and liver toxicity, may occur at any time. Myelotoxicity (leading to anemia, leukopenia or thrombocytopenia) often occurs early (≤8 weeks), although it may develop even after years [184]. Although leukopenia, particularly lymphopenia, is considered a marker of responsiveness, an excessive suppression of leukocyte count may lead to infections. The incidence of myelotoxicity has been estimated to be approximately 3% per year of treatment [185].

The risk of myelotoxicity is influenced by the activity of the enzyme thiopurine methyl transferase (TPMT), which catalyzes the methylation of 6-mercaptopurine to 6-methylmercaptopurine (6-MMP) [186,187]. Subjects with genetically determined negligible TPMT activity have diminished or absent 6-MMP levels and consequently higher rates of conversion of 6-mercaptopurine into 6-thioguanine [186–189]. 6-Thioguanine levels have been associ-

ated with thiopurine efficacy, while 6-MMP levels are associated with drug-related toxicity [190–192]. Testing for TPMT activity has therefore been suggested to predict thiopurine toxicity, including bone marrow suppression [191,193,194], although with conflicting findings [195,196]. The cost-effectiveness of TPMT testing [197,198] needs to be re-evaluated [199–202].

Liver toxicity, seen as elevations in serum levels of transaminases or cholestatic enzymes, develops in up to 12% of patients [203] and is related to high levels of 6-MMP [190,191,194]. Dose reduction may reverse this AE, and a meta-analysis suggested that shifting from azathioprine to 6-mercaptopurine is effective [204,205]. Mercaptopurine-induced hepatoportal sclerosis, leading to portal hypertension, is occasionally observed [206]. No recommendations for preventing fibrosis and portal hypertension in non-cirrhotic patients using long-term thiopurine therapy are available.

Nodular regenerative hyperplasia occasionally occurs in patients taking thiopurines. The cumulative incidence at 5 and 10 years is 0.6% and 1.28%, respectively, but the risk of this complication is higher in patients taking higher doses. Nodular regenerative hyperplasia, however, also occurs in thiopurine-naïve IBD patients with an incidence of 6%; IBD may be an independent predisposing risk factor to this condition [207].

6.1. Risk assessment for thiopurine AEs

Full blood count, liver function tests, and screening for viral infections (HIV, HCV, HBV) should be done before prescribing thiopurines. Liver function tests and full blood count should be done frequently in the first 2 months. A single schedule for laboratory assessments during treatment is not available, as national associations provide different recommendations. A general recommendation is a tighter surveillance during the first 1–2 months, with longer intervals thereafter (full blood count every 2–3 months). Severe leukopenia (neutrophils <1000/mm^3) requires immediate drug discontinuation, as does mild leukopenia (WBC <3000/mm^3 or neutrophils <2000/mm^3) occurring very early during treatment. Differently, mild leukopenia occurring during long-term treatment may be managed with dose reduction and strict monitoring [178,202].

In HBsAg-positive patients, antiviral therapy is recommended. In "isolated" anti-HBc-positive patients, transaminases and HBV DNA should be assessed every 3 months [208].

6.2. Thiopurines in combination therapy

Thiopurines are frequently combined with 5-ASA in IBD. This combination has been associated with enhanced thiopurine toxicity, due to the concomitant effect of 5-ASA on erythrocyte 6-thioguanine levels [209,210]. The clinical relevance of this effect is not clear, and current data do not support the need to avoid this combination.

The combination of low-dose thiopurines and allopurinol has been suggested to reduce the risk of hepatic and non-hepatic AEs. Allopurinol may inhibit the enzyme xanthine oxidase involved in the generation of 6-MMP [211,212]. Current evidence, however, does not support the use of this combination.

6.3. Thiopurines and opportunistic infections

Thiopurine-treated IBD patients have a 3-fold increased risk of opportunistic infections, while IBD patients receiving thiopurines and steroids have a 5-fold increased risk [103,213,214]. A broad spectrum of opportunistic infections has been reported, varying from mild to lethal. These include: viral infections with Epstein-Barr virus (EBV), cytomegalovirus, herpes simplex, varicella-zoster

and parvovirus; bacterial infections with *Listeria monocytogenes* or *Mycobacterium tuberculosis*; and fungal infections with *Pneumocystis jiroveci* or *Aspergillus fumigates*. Viral infections and sepsis represent additional RISK factors for myelosuppression. The hemophagocytic lymphohistiocytic syndrome associated with a high mortality (≤30%) may complicate these infections in patients using thiopurines [215].

6.4. Thiopurines and cancer risk

Since the 1980s, a relation between lymphoma and thiopurine use has been postulated in IBD patients, who are already at increased lymphoma risk [216–219]. Although azathioprine increases the life expectancy (0.04 years) and the quality of life [220] of CD patients, this gain decreases with increasing age and the lymphoma risk. Thiopurines are associated with EBV-positive lymphoma in IBD [221]. In 2003, a meta-analysis found an increased lymphoma risk in IBD patients using thiopurines, with a standardized incidence ratio of 4.18 (95% CI, 2.07–7.51) despite marked heterogeneity among studies [222]. A subsequent prospective observational study confirmed, in France, the higher incidence of lymphoproliferative disorders in patients receiving thiopurines than in those who discontinued or never received thiopurines; this risk increased with age and years of treatment [223]. A single-center Dutch study also reported a significantly increased lymphoma risk in IBD, with a correlation between EBV-positive lymphoma and thiopurines [224]. A rare, often fatal hepatosplenic T-cell lymphoma has been reported in patients using azathioprine, particularly when combined with TNFα antagonists (see Section 10).

An association between thiopurine use and non-melanoma skin cancer (NMSC) has been reported in CD [225–229]. In some studies [225–228], the incidence of NMSC was higher in IBD patients than in controls; in one of these studies, the incidence rate ratio was 1.64 [225]. However, use of thiopurines further increased this risk (OR, from 3.56 to 4.27) [226–229]. A meta-analysis found, instead, that the risk of NMSC is only modestly elevated in IBD and argued that the discrepancies between population- and hospital-based studies were evidence of ascertainment bias [229].

Recently, a prospective observational study found that IBD patients receiving thiopurines had an increased risk of urinary tract cancers: the multivariate, adjusted hazards ratio between patients who received and those who did not receive thiopurines was 2.82 (95% CI, 1.04–7.68) [230]. Clinically relevant excess risk was observed in older men [230].

6.5. Surgery

Thiopurine monotherapy in IBD patients undergoing elective surgery is not associated with an increased risk of complications [231,232].

6.6. Pregnancy and breastfeeding

Azathioprine and 6-mercaptopurine are category D drugs for pregnancy and lactation (Table 2). However, this classification is based on old studies concerning high doses of thiopurines for leukemia [233]. Although few data are available, clinical trials and case series suggest that thiopurines are safe in pregnancy and lactation [234–236].

An increased risk of preterm birth was reported in pregnant patients using thiopurines, together with higher risk of anemia, pancytopenia and alkaline phosphatase elevation in babies exposed to thiopurines in utero. However, evidence is conflicting [237]. In clinical practice, IBD activity, rather than thiopurine use, appears to be the major risk factor for complications during pregnancy and

delivery. Therefore, thiopurine withdrawal is not recommended in patients at high risk for relapse. No increased risk of congenital abnormalities has been observed in children whose fathers were taking thiopurines at conception [238–240].

Statement 15
Thiopurines may induce adverse events in up to 30% of patients even in the short term, requiring drug discontinuation [EL2]. Myelotoxicity, hepatitis and acute pancreatitis are the most relevant side effects [EL2]. Thiopurine use is associated with an increased risk of non-melanoma skin cancer and lymphoma [EL1].

Statement 16
Switching to 6-mercaptopurine is a possible strategy for patients with azathioprine intolerance to avoid most AEs except for acute pancreatitis or bone marrow suppression [EL4].

Statement 17
Full blood count and liver function tests as well as HIV, HCV and HBV screening are indicated before starting thiopurines [EL5].

Statement 18
In HBsAg-positive patients, antiviral therapy is recommended. In "isolated" anti-HBc-positive patients, transaminases and viremia (HBV DNA) should be assessed every 3 months, but antiviral therapy is recommended only if viremia is detected [EL5]. There is insufficient evidence on which to base a recommendation for how long to treat these patients [EL5].

Statement 19
There is insufficient evidence regarding the ideal duration of treatment with thiopurines, although prolonged treatment (>5 years) can be considered on a case-by-case basis [EL4]. In patients starting thiopurines, liver function tests and full blood count should be done frequently in the first 2 months. Thereafter, full blood count should be monitored every 2–3 months but the optimal timing for liver function testing is not established [EL5]. Dose reduction or discontinuation is indicated in cases of bone marrow or liver toxicity [EL5]. Pancreatitis requires drug discontinuation [EL1].

Statement 20
Thiopurines are contraindicated in patients with active infections or neutropenia (neutrophils <1000 mm^3) [EL1]. Thiopurines should be used with caution in patients with a history of neoplasia [EL5]. Thiopurines should be used with caution in elderly patients and EBV-negative young men, due to their increased risk of lymphoma [EL2].

Statement 21
Thiopurines are generally safe during pregnancy and lactation [EL2], although an increased risk of preterm births has been observed [EL2]. Male patients should not stop therapy when planning to procreate [EL5].

7. Methotrexate

Methotrexate may induce gastrointestinal intolerance, hepatic toxicity, bone marrow suppression, and hypersensitivity pneumonitis. Nausea and vomiting occur in up to 40% of IBD patients treated with methotrexate [21,241] and may require drug discontinuation. Folic acid supplementation may reduce the incidence of gastrointestinal symptoms [242].

Hepatic fibrosis is the most significant AE of methotrexate use, and is correlated with long-term treatment. This observation comes from a study of psoriatic patients who took methotrexate daily, leading to high hepatic drug concentrations and a high frequency of liver damage, with cirrhosis or active hepatitis seen in up to 23% of cases [243]. High intrahepatic concentrations are not achieved in patients who follow a once-weekly schedule [244]. This may account for the low prevalence of hepatic toxicity in RCTs and case series of IBD patients, indicating that the reversible elevation of transaminases is the most frequent AE in methotrexate-treated IBD patients [245–247]. In a meta-analysis, the pooled incidence

rate of abnormal aminotransferase levels (≤2-fold increase) in methotrexate-treated patients was 1.4/100 person-months, while the rate of hepatotoxicity (≥2-fold increase) was 0.9/100 person-months [248].

Methotrexate-induced pathological liver changes in IBD have been investigated in few studies. In one study of 11 patients treated for a median of 18 months (range 7–58) with a mean cumulative dose of 1225 mg (range 220–3400 mg), there were 5 cases of mild steatosis and one case each of granulomatous hepatitis with mild portal fibrosis, slight sinusoid dilation, and periportal fibrosis, while a normal biopsy was reported in the remaining three cases [249]. In another study, 20 patients had liver biopsy after a mean methotrexate duration of 131.7 weeks (range 66–281) and a mean cumulative dose of 2633 mg (range 1500–5410 mg): biopsy was normal or showed Roenigk's grade I histological changes in 17 patients (85%) while the remaining 3 patients had grade II–IIIb changes [250]. Abnormal serum transaminase levels are not predictive of hepatic histological changes [250]. Alcohol consumption, obesity, diabetes mellitus, >1500 mg dose and frequent dosing intervals are risk factors for liver injury in psoriatic patients [243]. Prophylactic folate supplementation may reduce hepatic AEs, although controlled studies have not been done in IBD patients. Reactivation of HBV infection has been reported in rheumatic diseases [251], but again data in IBD are lacking.

The extent of liver fibrosis in IBD patients treated with methotrexate can be assessed by "transient elastography" using a FibroScan device. However, in one series [252], FibroScan findings did not correlate with the cumulative methotrexate dose, suggesting the need to reconsider total dose as a risk factor for hepatic fibrosis in IBD.

The American College of Rheumatology recommends liver biopsy before treatment with methotrexate if chronic liver disease is suspected [253]. Liver biopsy during treatment is recommended when aspartate aminotransferase (AST) levels are high throughout the year (repeated every 4–8 weeks) and in cases of hypoalbuminemia. Dose reduction is recommended in cases of high AST, while moderate-to-severe fibrosis or cirrhosis requires discontinuation.

7.1. Pregnancy and breastfeeding

Methotrexate is embryotoxic and absolutely contraindicated during pregnancy (FDA pregnancy category X), as it causes severe malformations including anencephaly, hydrocephaly and meningomyelocele [254]. Craniofacial and limb defects are also possible. Adequate contraception must be used by women of childbearing age during treatment, and methotrexate should be stopped ≥3 months before planning a pregnancy. In this period, folate supplementation is strongly recommended.

The incidence of myelosuppression and hypersensitivity pneumonitis in IBD patients taking methotrexate has not been reported. Myelotoxicity was observed in 4.5% of patients in a multicenter retrospective study, after a median treatment duration of 17 months [255].

Statement 22
Gastrointestinal intolerance is observed in up to 40% of patients treated with methotrexate, and is reversible upon drug discontinuation [EL1]. Oral folic acid administration [EL1] and dose fractionation [EL4] can reduce the incidence of methotrexate-induced gastrointestinal intolerance.

Statement 23
A complete medical history, including daily alcohol intake and serology for HBV and HCV, must be obtained before initiating methotrexate treatment [EL5]. Routine blood testing, including complete blood count and serum transaminases, is recommended in patients treated with methotrexate, and should be done at baseline, after 4 weeks of treatment, and then every 12 weeks [EL4].

Statement 24

Methotrexate therapy is contraindicated in patients with active viral hepatitis, severe fibrosis or cirrhosis (stages F3 or F4 on the METAVIR scoring system), or chronic HBV infection [EL4]. A pretreatment liver biopsy should be performed in patients with suspected chronic liver disease [EL4].

Statement 25

Methotrexate treatment is frequently associated with a slight increase in serum transaminases (up to 2-fold above normal range) [EL1]. This change is not predictive of significant liver toxicity and fibrosis and does not warrant drug discontinuation [EL4].

Statement 26

Methotrexate should be discontinued in cases of a persistent, significant increase of serum transaminases (≥2-fold above the upper limit of normal over a period of 4 weeks) [EL4]. A significant increase in serum transaminases, which persists following drug discontinuation, or the development of clinical or laboratory signs of chronic liver disease is an indication for liver biopsy [EL4].

Statement 27

Non-invasive evaluation of liver fibrosis may be a useful tool to monitor liver fibrosis in IBD patients receiving methotrexate treatment [EL3].

Statement 28

Methotrexate is embryotoxic and absolutely contraindicated in the pre-conception period for men and woman and during pregnancy [EL1]. Adequate contraception must be used by women of childbearing age if they wish to take methotrexate. Before conception, methotrexate must be avoided for 3–6 months.

8. Cyclosporine A

Cyclosporine A (CsA) can cause dose-dependent and dose-independent AEs. Dose-dependent AEs associated with CsA use include renal toxicity, hypertension, lymphoma, infections, seizures, paresthesias hypertrichosis, and anaphylaxis. In older studies, where >5 mg/kg day CsA was administered, 329 AEs were reported in 343 patients (0.94 AE/patient) [256]. This rate can be markedly reduced by monitoring the serum concentration of CsA every other day and maintaining blood levels between 100 and 450 ng/ml [22,257]. A double-blind RCT that compared clinical outcomes between patients who received intravenous CsA at 2 or 4 mg/kg found a further, although not significant, reduced incidence of AEs in the 2 mg/kg group [23]. The lower dose has thus been preferred.

Cholesterol levels should be assessed before therapy. CsA blood levels require regular monitoring since, after oral administration, CsA metabolism and absorption may show wide interindividual variations [256].

8.1. Opportunistic infections

High-dose CsA (>5 mg/kg day) is associated with infectious complications, including *P. jiroveci* pneumonia, herpes esophagitis, mycotic aneurysm, and staphylococcal sepsis [256]. Concomitant corticosteroids or thiopurines increase the risk. *P. jiroveci* prophylaxis is recommended when using ≥1 immunosuppressive drug (calcineurin inhibitor or TNFα antagonist) [104,258]. In a retrospective UC cohort (76 patients who received either 4 mg/kg intravenously or 5 mg/kg orally), with an up to 7-year follow-up, no infections were reported and CsA was stopped in only 4 cases for noninfectious AEs (seizures, urticaria, renal failure or hypertension) [259].

8.2. Cancer risk

Malignancies are more frequent in patients with renal, heart or liver transplantation after long-term treatment with CsA than in transplant recipients who did not take CsA. The increased risk is related to CsA dose and duration, and is lower than that observed in transplant recipients using thiopurines or tacrolimus [260]. Fewer malignancies were observed using lower CsA doses (<5 mg/kg day) [261]. As these data refer to transplant recipients and patients with other imune-mediated diseases, these conclusions may not apply to IBD patients. An increased risk of NMSC has been documented in CsA-treated patients with psoriasis or rheumatoid arthritis [262], but not in CsA-treated IBD patients [263]. In solid organ transplant recipients, CsA use leads to a 200-fold increase in skin cancer, particularly squamous cell cancer [264,265]. Low-doses (75–125 ng/ml) were associated with significantly fewer malignancies [266].

8.3. Surgery

CsA does not increase the risk of peri-operative or postoperative complications in adult UC patients [25,267,268].

8.4. Reproductive health

CsA and modified CsA (Neoral) did not have significant effects on female or male fertility in transplant series [269,270]. CsA is a FDA pregnancy category C drug (Table 2). This treatment does not increase the risk of congenital malformation, but it does slightly, but not significantly increase the risk of premature delivery and low birth weight [271,272]. It is unclear whether these findings are related to CsA or the underlying disease. Case reports and small series support the safety of CsA in pregnant patients with severe IBD [273]. CsA may therefore be used as rescue therapy during pregnancy in severe, refractory IBD.

CsA is excreted at a small rate into breast milk [172]. The American Gastroenterological Association considers CsA use during lactation to be safe [172]. Nonetheless, breastfeeding by women taking CsA is discouraged due to the potential induction of immunosuppression in the newborn.

Statement 29

In the case of idiosyncratic AE, a switch from parenteral to oral CsA appears to be safe [EL4].

Statement 30

Regular monitoring of serum levels of CsA is recommended [EL2]. Cholesterol should be checked before the institution of therapy. Fasting blood glucose, electrolytes (including magnesium), renal function and blood pressure should be monitored every 2 days and fortnightly for intravenous and oral administration, respectively [EL3].

Statement 31

The use of 2 mg/kg CsA is recommended for minimizing the risk of AEs [EL1]. P. jiroveci prophylaxis is recommended in patients on combined immunosuppressive therapy [EL1].

Statement 32

CsA may be administered during pregnancy in cases of severe refractory IBD as a rescue therapy [EL4]. CsA is secreted to some extent into breast milk but is likely to be safe to infants. Nonetheless breastfeeding should be discouraged due to the potential immunosuppressive effects on the newborn [EL4].

9. TNFα antagonists

TNFα antagonists authorized for treating IBD in Italy currently include infliximab (i.v.), adalimumab (s.c.) and, more recently, golimumab (s.c.) and infliximab biosimilars (i.v.).

9.1. Infusion and injection site reactions

Infusion reactions to infliximab present as a wide range of signs and symptoms within 2 h of administration [274]. These reactions are more frequently observed in clinical trials (7%–10%) [27,275,276] than in clinical practice (3.8%–10%) [277–281]. Mild-moderate reactions to infliximab resolve spontaneously when the infusion is slowed or stopped. Severe reactions occur in ≤5% of patients [282], may be life-threatening, and are more frequent during episodic than scheduled maintenance regimens [282–286].

Infusion reactions are more frequent in patients with anti-infliximab antibodies. In a meta-analysis [287], the pooled relative risk (RR) was 2.4 and the NNH was 6. However, data are conflicting, possibly due to different tests for anti-infliximab antibodies [288,289]. Most of the severe reactions appear unrelated to IgE-mediated mechanisms but to anti-infliximab IgG [282,290,291]. The risk of reaction is higher during re-initiation therapy [291].

Measuring levels of anti-infliximab antibodies before infliximab re-induction is of limited utility, as seronegativity does not exclude reactions [282,292]. Whether concomitant immunosuppressive use prevents the development of anti-infliximab antibodies is debated [277,278,281,282,292]. In patients who tolerate 2-h inflix-imab infusions, a 1-h infusion appears safe [293]. Reactions are successfully treated using antihistamines, acetaminophen or corticosteroids. Steroid premedication and antihistamine treatment reduce anti-infliximab antibody levels, but do not prevent reactions [294,295]. Patients with mild-moderate reactions can be retreated using premedication (steroids and antihistamines) [279]. Severe reactions require careful reconsideration regarding the risks and benefits of infliximab.

Adalimumab and golimumab cause mild-moderate injection site reactions at a variable frequency (4%–38%) [28,296–299]. Severe systemic hypersensitivity is rare [278,300–302]. Recently, golimumab was shown to have the same safety profile as other TNFα antagonists [278,298,299,302]. Infliximab biosimilars and infliximab have the same type and frequency of local and systemic AEs [302–308].

9.2. Autoimmunity and delayed hypersensitivity reactions

Delayed hypersensitivity reactions (DHR) or, more appropriately, "serum sickness-like reaction", are myalgia, arthralgia, fever or rash occurring within 14 days of infliximab administration [274,309]. In clinical trials, severe DHR were reported in 0.8% [27] and 3% [275] of patients. In retrospective studies, a higher occurrence has been reported (2.8%–7%), generally after infliximab discontinuation over 12 weeks [277,287]. The role of anti-infliximab antibodies in DHR is debated [281,310]. Only a minority of patients with DHR underwent infliximab retreatment [281,310]. Patients with severe reactions to infliximab require steroids, paracetamol and antihistamines, which lead to resolution within 1–2 weeks [6].

9.3. Skin reactions

Skin reactions associated with anti-TNFα treatment occur in about 1.5% of patients and include microbial eczema, pityriasis versicolor, herpes simplex reactivation, tinea corporis, and acute staphylococcal infection [311]. Acute reactions at the injection site or after infusion are as frequent as 1% [312].

ANA seroconversion occurs in around 1% of IBD patients using anti-TNFα; this rate is lower than that observed in similarly treated patients with rheumatoid arthritis [312]. Drug-induced systemic lupus erythematosus may also occur: this syndrome cannot be prevented, but it is self-limiting in 94% of cases [313].

It has been known for a long time that the prevalence of psoriasis is higher in IBD patients than in the general population [314]. These two diseases share a common genetic background [315]. Paradoxical skin inflammation with "de novo" development of psoriasis has been observed in patients using TNFα antagonists [316–325], with reported incidences of 1/1000 patient-years [324] and around 3% [325–327]. Psoriasiform skin reactions show a specific immunologic pattern [328] and respond to ustekinumab [328]. Dermatologic assessment is advisable.

Other rarer dermatological reactions associated with anti-TNFα treatment are alopecia, lichenoid reactions, eczema, vitiligo, acneiform eruptions, vasculitis, granuloma annulare, and interstitial granulomatous dermatitis [311,329].

9.4. Rare AEs

Non-infectious hepatitis, sometimes diagnosed as autoimmune hepatitis, is rare and mostly observed in rheumatological or dermatological diseases [330–334]. TNFα antagonists may improve hepatic function in IBD patients [335]. Liver deterioration during anti-TNFα treatment is more likely related to worsening of the underlying hepatic disease [335].

Occasionally, bone marrow toxicity (neutropenia, thrombocytopenia and anemia) may occur during anti-TNFα treatment. Transient neutropenia has been reported in up to 16% of patients [336,337]. Increased hemoglobin levels have also been reported [338,339]. TNFα antagonists may cause neurologic symptoms related to demyelination and worsening of preexisting multiple sclerosis [340–344]. The relationship between neuropathies and TNFα antagonists is not defined.

9.5. Safety of switching therapies

Switching between anti-TNFα agents is frequently done when a patient stops responding to one agent. No specific safety concerns have been reported regarding this practice [345]. Some AEs are "class effects" common to all anti-TNFα agents, and therefore recur after the switch.

9.6. Laboratory testing during treatment

No specific recommendations have been established for biochemical monitoring during anti-TNFα treatments [36,346–349]. We suggest that, in the absence of signs or symptoms requiring specific investigations, full blood count, liver function tests, and laboratory tests for serum C-reactive protein, creatinine and ferritin should be done every 2–3 months. HBV-DNA should be monitored in patients with a possible occult HBV infection, while HIV re-testing is indicated for patients at risk. Screening for C. difficile is recommended at every flare. Patients traveling to endemic areas should be rescreened for latent tuberculosis when they return [350].

9.7. Opportunistic infections

In rheumatoid arthritis, TNFα antagonists are associated with an increased risk of opportunistic and serious infections [351–354]. In CD, a 2-fold increased risk of opportunistic infections and an increased risk of serious infections (albeit lower than that observed with corticosteroids) have been reported [355–357]. Age is an independent risk factor [358–360].

The risk of post-operative infectious complications using TNFα antagonists is debated. Some studies and meta-analyses showed an increased risk (especially in CD) [361–363], while others did not, emphasizing other risk factors, including steroid use and low serum albumin [364–366].

9.8. TNFα antagonists and cancer risk

The cancer risk using anti-TNFα treatments has been extensively investigated [367–404], but several issues are still debated.

For lymphoma, the FDA reported a standardized incidence ratio (SIR) for non-Hodgkin's lymphoma of 6.4 using infliximab and 5.5 using adalimumab [368]. In CD, values of SIR between 3.23 and 5.5 have been reported [369,370]. However, the lymphoma risk may be higher in subgroups of patents, particularly those with CD [371], although with conflicting evidence [372,373]. As TNFα antagonists are frequently combined with thiopurines, increasing the lymphoma risk, the risk associated with anti-TNFα monotherapy is difficult to estimate [206,374]. Recently, TNFα inhibitors, when used alone without thiopurines, were reported to not increase the lymphoma risk [375–379]. Hepatosplenic T-cell lymphoma (HSTCL) has been reported in IBD patients, particularly young men with CD treated with combined thiopurines and TNFα antagonists [380–382]. Rare cases of HSTCL were reported in patients using azathioprine, but not anti-TNFα monotherapy (see Section 10) [380–382].

Regarding NMSC, conflicting results exist on the risk in rheumatoid arthritis patients using TNFα antagonists [383–386]. In IBD, a recent meta-analysis reported a 37% excess risk of melanoma [387]. An excess risk of both melanoma (RR = 1.29) and NMSC (RR = 1.46) was observed in a large cohort of IBD patients in the United States [388]. A Cochrane meta-analysis [389] and an evaluation of the TREAT registry [390] both found no increased rate of skin cancer in IBD patients treated with anti-TNFα. However, using TNFα antagonists appeared to increase the melanoma risk (OR 1.88) [388]. Similarly, a systematic review reported a 2-fold risk of NMSC in patients using anti-TNFα monotherapy [391].

Some studies have assessed the overall risk of cancer associated with anti-TNFα use. A meta-analysis of rheumatoid arthritis patients [392] found an overall increased cancer risk (RR = 3.3), but this finding has not been confirmed by meta-analyses [388,393] and treatment registries [394,395]. In IBD, no increased risk of malignancy using TNFα inhibitors vs. placebo was detected in a meta-analysis of 10 trials [396]. Regarding the cancer risk in the long-term, the TREAT registry, which included over 6000 CD patients followed for >5 years, detected no difference in the unadjusted incidence of neoplasia between patients treated with infliximab and other therapies [355,397]. Similarly, a retrospective analysis of four data sets from the United States did not detect an association between TNFα inhibitors and malignancy among 6357 IBD patients [398]. An Italian multicenter long-term matched pair study reported comparable frequencies of neoplasia in CD patients treated or not with infliximab [399,400]. These observations have been confirmed by several studies and meta-analyses [401–403], indicating that anti-TNFα monotherapy does not increase the overall cancer risk.

More information on the risk of cancer in CD and UC patients treated with TNFα antagonists comes from a recent multicenter nested case-control study conducted by the IG-IBD [404]. This study found that, in CD, the combined use of TNFα antagonists and thiopurines was a risk factor for cancer overall (OR 1.97) and for extracolonic cancer (OR 2.15). It also found that penetrating disease was a risk factor for cancer overall and for extracolonic cancer. In UC patients, immunomodulators were not identified as risk factors for cancer, while clinical characteristics did associate with cancer risk.

9.9. Pregnancy and breastfeeding

Infliximab, adalimumab and golimumab are FDA pregnancy category B drugs (Table 2). However, they cross the placenta, especially in the second and third trimesters [405,406], and detectable serum levels can persist in newborns up to 6 months after birth.

No increased risk of congenital abnormalities has emerged in several cases series and patient registries [407–415].

A recent prospective study of women taking anti-TNFα treatments during pregnancy reported comparable rates of infection, allergies, eczema and adverse reactions to vaccines in the newborn infants of both mothers who stopped treatment in the third trimester and those who continued [416]. These rates were also similar to those in children of non-IBD women at the 1-year follow-up [416].

LIVE vaccines (poliovirus, rotavirus, BCG) should be avoided in children with in utero exposure to biologics until at least 6 months of life [416]. However, a recent prospective study found that, when women were treated with adalimumab or infliximab during pregnancy, the anti-TNFα agent was detected in their infants until 12 months of age [415]. Combined treatment with anti-TNFα and thiopurines during pregnancy increased the risk of infant infections beyond that associated with anti-TNFα monotherapy, suggesting that the administration of live vaccines should be avoided until the infants are older than 1 year [415].

Statement 33

Infusion-related reactions to infliximab are common but are less frequent during scheduled maintenance regimens than episodic regimens. Severe reactions are uncommon but may lead to treatment discontinuation [EL1]. Pretreatment with antihistamines or steroids does not prevent the development of infusion reactions [EL2]. Injection site reactions to adalimumab and golimumab are usually mild and do not require drug discontinuation [EL2].

Statement 34

The most common cutaneous AEs of anti-TNF treatments are skin infections [EL2] and psoriatic manifestations [EL2]; much rarer are drug-induced systemic lupus erythematosus [EL3] and other dermatological conditions.

Statement 35

Rare potential AEs of anti-TNF agents are non-infectious hepatitis [EL4] and reduced blood cell counts (anemia, neutropenia, thrombocytopenia) [EL4].

Statement 36

Although neurological AEs associated with anti-TNFα treatment are rare, it is important to monitor signs and symptoms suggestive of a demyelinating disorder [EL5]. Patients with a history of demyelinating disease or with symptoms of polyneuropathy should be carefully evaluated before initiating anti-TNFα therapy [EL5].

Statement 37

When switching from one anti-TNF treatment to another due to loss of response, there are no additional safety concerns [EL1]. In case of anti-TNF class AEs, switching should be avoided as the risk of recurrence of the AE will be the same [EL5].

Statement 38

During anti-TNFα therapy, even in absence of alarming signs and symptoms, periodic laboratory investigations are advisable depending on the patient's conditions and risk factors [EL5].

Statement 39

Data from registries and RCTs indicate a significantly increased risk of opportunistic infections with anti-TNFα therapy [EL1]. Older age is an independent risk factor [EL3]. Data on the risk of postoperative infections are conflicting, but most series demonstrated an increased risk in CD [EL2].

Statement 40

Anti-TNFα agents used in monotherapy do not seem to increase the rate of lymphoma, including hepatosplenic T-cell lymphoma, in adults or children [EL1].

Statement 41

Data on the risk of skin cancer in IBD are limited, conflicting, and complicated by confounders (e.g. thiopurine use). However, an up to

2-fold increase in melanoma and NMSC has been reported, requiring vigilance and regular skin examinations [EL2].

Statement 42

Although long-term studies in IBD are few, no clear overall increased risk of solid malignancy has been reported during anti-TNFα therapy [EL1].

Statement 43

The use of anti-TNFα agents during pregnancy presents a low risk, but these drugs should be withdrawn in the third trimester [EL2]. Due to potential presence of these drugs in breast milk, physicians should discuss the risks of breastfeeding with mothers [L5]. LIVE vaccines in newborns with in utero exposure to biologics should be avoided for at least 6 months of life [EL2].

10. Combination therapy

10.1. Infusion reactions

Patients treated with infliximab may develop specific antibodies to this drug [417], but this risk can be reduced by adding a thiopurine [275,276]. Whether concomitant immunosuppression reduces the frequency of infusion reactions is debated [278,281,282].

10.2. Infections

Immunomodulators increase the risk of infections. Corticosteroids have been associated with fungal infections, thiopurines with viral infections, and anti-TNFα with fungal and mycobacterial infections [417]. When these treatments are combined, the frequency of infections may increase. Combined immunomodulators HAVE been associated with an increased risk of opportunistic infections: 3-fold increased risk using 1 immunomodulator and 14.5-fold using $\geq$2 immunomodulators [268].

10.3. Cancer risk

A pooled analysis of clinical trial data from 1594 CD patients treated with adalimumab found a greater overall incidence of malignancy (SIR 3.04) and a higher incidence of NMSC (SIR 4.59) in patients using combined thiopurine and adalimumab (but not adalimumab monotherapy) than in the general population [418]. Additionally, patients who received combination therapy had an overall higher risk of malignancy (RR = 2.82) and of NMSC (RR = 3.46) than did patients on adalimumab monotherapy. Only 2 cases of lymphoma were recorded in the combined series [418]. These results on the safety of adalimumab monotherapy must be considered in light of several limitations of the analyzed data, namely: (a) the absence of a group using immunomodulators as monotherapy; (b) the non-IBD population is an imperfect comparator for IBD patients treated with 1–2 immunomodulators; and (c) immunomodulator use was defined only at baseline (possibly underestimating the cancer risk).

Our recent multicentre nested case-control study [404] found an increased overall cancer risk in patients using combination therapy with thiopurines and TNFα antagonists. This increase was greatest in patients with perforating CD [404]. In contrast, an analysis of the TREAT registry showed that there was no increase in cancer risk using immunomodulators, infliximab, or combination therapy [397]. Long-term multicenter studies are required to clarify this issue.

In 2009, a meta-analysis of 8905 CD patients treated with anti-TNFα, with or without thiopurines, concluded that although combination therapy increased the risk of non-Hodgkin's lymphoma, the absolute rate is low and should be weighed against the drugs' efficacy [370]. In 2011, a US study of >15,000 IBD patients confirmed that combined anti-TNFα and thiopurines, but not IBD itself, increases the lymphoma risk [381]. The most common lymphoma subtypes were diffuse large B-cell lymphoma (44%), follicular lymphoma (14%), and Hodgkin's lymphoma (12%). A French study reported a higher RR of lymphoma in patients using combination therapy than anti-TNFα monotherapy [418]. However, no study directly compared the lymphoma risk from combination therapy with that from anti-TNFα monotherapy.

The occurrence of HSTCL has been reported in IBD patients treated with combined thiopurines and TNFα antagonists, particularly in young (<35 years) men with CD [347,371,382,419–422]. According to a systematic review published in 2011 [381], more than 10% of the approximately 200 cases of HSTCL described worldwide had been reported in IBD patients, all treated with immunomodulators (n = 36). All 36 IBD patients who developed HSTCL had a history of thiopurine use, 16 as monotherapy and 20 in combination with TNFα inhibitors. No HSTCL case has been observed among IBD patients using anti-TNFα monotherapy [381,382]. Among the 36 IBD patients discussed in the review [381], 27 had CD, 29 were male, their median age at diagnosis of HSTCL was 22 years, 37 were deceased at the time of the study, and the median duration of thiopurine exposure was about 5 years (range, 1–7). These data strongly support the use of combination therapy in carefully selected patients and only when a clear benefit is expected, particularly in young male CD patients. They also support the avoidance of early combined treatment in young IBD patients and the shift to thiopurines or TNFα antagonists, according to response [379,423].

Thiopurines (but not TNFα antagonists) appear to increase the risk of NMSC, particularly in patients with CD, which itself increases risk of this skin cancer [432]. A nested case-control study failed to show a further increased risk in IBD patients with recent or persistent combination therapy [393]. An analysis of the FDA Adverse Event Reporting System found that both anti-TNF-α monotherapy and combination therapy with thiopurines increase the risk of melanoma and NMSC in IBD patients [424]. Dermatologic screening has been suggested for all patients undergoing anti-TNFα treatment [425,426]. A meta-analysis of 14,590 IBD patients from 49 RCTs of biologics (adalimumab, certolizumab, golimumab, infliximab, natalizumab, vedolizumab) reported a moderately increased risk of any infection (OR [95% CI]: 1.19 [1.10–1.29]) and a substantially increased risk of opportunistic infections (OR 1.90 [1.21–3.01]) using these drugs [302]. Differently, no increased risk of serious infections or malignancy (OR 0.90 [0.54–1.50]) was found [302].

Findings from a recent meta-analysis of 16 studies suggested similar rates of cancer recurrence among individuals with prior cancer treated or not with anti-TNF monotherapy, immunomodulators, or combined treatments [427]. Additional large, prospective studies are required to clarify this relevant issue.

Statement 44

Concomitant use of immunomodulators reduces the development of anti-infliximab antibodies [EL1]. The role of concomitant immunosuppression is controversial even if it seems to reduce drug reactions during infliximab infusion [EL1].

Statement 45

The risk of opportunistic infections is higher in patients treated with combinations of immunomodulators and anti-TNFα agents [EL1]. It is not clear whether this risk s related to the biologics, to the immunomodulators, to both, or to other factors such as the severity of disease [EL3].

Statement 46

The overall risk of lymphoma appears to be increased in patients treated with anti-TNF agents in combination with thiopurines [EL1], although the absolute risk is very low [EL1]. Combined treatment with thiopurines and adalimumab is associated with an increased risk

of NMSC and other cancers [EL2]. Combined maintenance treatment with anti-TNF agents and thiopurines should be avoided, particularly in young patients, because of the risk of hepatosplenic T-cell lymphoma [EL4]. Combination therapy should be reserved for high-risk patients. Whether a previous history of cancer is a contraindication for combination therapy is controversial. In these patients, the decision should be made on a case-by-case basis[EL5]. The implementation of conventional screening tests, like those commonly used before the administration of anti-TNF monotherapy, is recommended before the prescription of combination therapy [EL5].

11. Vedolizumab

Vedolizumab is a new immunomodulator effective in moderate-severe IBD [34,428,429]. In Italy, vedolizumab was approved in 2016. Vedolizumab binds to α4β7 integrin, and subsequently inhibits leukocyte adhesion and migration from the vascular endothelium into the diseased gut. Current data support the safety of vedolizumab in IBD patients [426,430–433]. Low frequencies of serious infections, infusion-related reactions, malignancies and other AEs have been observed with vedolizumab [430–433]. However, a longer follow up is required. Several trials [34,428,429,434] and meta-analyses [426,435] support the favorable risk profile of vedolizumab, with no increased incidence of serious AEs or serious infections compared with placebo. A low frequency (<6%) of AEs has been reported, including: headache, nasopharyngitis, nausea, arthralgia, upper respiratory infection and fatigue [431]. Therefore, vedolizumab use has been suggested for elderly IBD patients, who are at higher risk of infectious complications [436]. Vedolizumab use was not associated with progressive multifocal leukoencephalopathy [433], caused by JC virus reactivation, differently from natalizumab, a nonspecific antagonist of α4β7 and α4β1 integrins [437]. The FDA classifies vedolizumab in pregnancy category B (Table 2).

Conflict of interest

The study was not supported by any grant nor funded and any of the below reported disclosures are related to the study. *LB.* Lecture fees or Advisory Board: Zambon, MS&D, Takeda, Abbvie, Sofar, Ferring, Wassermann; *VA.* Consultant:: Abbie, Hospira, Mundipharma, MS&D, Takeda, Janssen, Ferring; Lecture fees: Abbvie, Ferring, Hospira, MS&D, Takeda, Medtronic, Menarini; Unrestricted research grants from: Giuliani, Ferring, Sofar, Roche, Gillead, MS&D, Abbvie, Otsuka; *SA.* Consultant to: Abbvie, Mundipharma, MS&D, Takeda, Recordati, Zambon; Unconditioned grants from: MS&D, Abbvie, Takeda, Mundipharma, Ferring, Sofar, Zambon. *AA.* Consulting and/or lecture fees: Abbvie, Astra, Biogen, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Pfizer, Samsung, Sofar, Takeda, Zambon. Research grant: MSD; *EC.* Lecture fees: Abbvie; *FC.* Consultant to: Mundipharma, Abbvie, MS&D, Takeda, Janssen, Roche, Celgene; Lecture fees from: Abbvie, Ferring, Takeda, Allergy Therapeutics; Unrestricted research grants: Giuliani, Sofar, MS&D, Takeda, Abbvie *FC.* Consultant to: MS&D, Takeda, AbbVie; Lecture fees: Abbvie, MSD, Takeda, Chiesi; Unrestricted research grants: AbbVie, Sofar, MS&D, Ferring. *M. Comberlato.* Consultant to: Abbvie, MS&D, Takeda, Sofar; Lecture fees: Abbvie, Ferring, MS&D, Takeda, Sofar *M. Cottone*: Grant master frpm: Takeda, Abbvie, Msd, Sofar. *SD.* Speaker, Consultant and Advisory Board: Abbvie, Ferring, Hospira, Johnson and Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim. *MD.* Lectures, board and/or congress fees: Abbvie, Pfizer, Takeda, Mundipharma, Janssen, MS&D, SOFAR, Ferring, Chiesi; *RDI.* Speaker and advisory board member: Abbvie, MSD, Zambon, Mundipharma, Hospira, Biogen, Takeda, Holstone *GF.* Grant/ research support: Giuliani, Abbott Laboratories (AbbVie), Takeda. *WF.:* Advisory boards: Abbvie, Mundipharma, speaker fees:

Takeda, Zambon, educational grant: MSD; *PG.* Consultant: Takeda, Abbvie, MSD, Biogen, Alfa Wassermann; speaker: Abbvie, Takeda, Ferring, Sofar, Chiesi. *AK* Scholarship by Abbvie. *GL.* Consultant: MSD Italy, Shire; Research grants : Giuliani Italy, Alfa Wassermann Italy. Sofar Italy. *GM.* Lecture fees or board for: Chiesi, MS&D, Mundipharma, Takeda, Zambon. *MM.* Lecture fees: Abbvie, MS&D, Takeda. *AO.* Lecture fees: Abbvie, Chiesi, MSD, Otsuka, Takeda, Sofar, Mundipharma: Consultant: Abbvie, MSD, Sofar ,Takeda. *C Papi.* Consultant or educational grants: Takeda, Abbvie, MSD Chiesi. Sofar, alfa Wassermann. *C. Petruzziello.* No disclosures. *F.R.* Consultant to: Abbvie, MSD, Takeda, Biogen, Hospira-Pfizer; Lecture fees: Abbvie, Ferring, Takeda, MSD, Sofar ; Unrestricted research grants: Takeda, Abbvie. *GR.:* Lecture fees: Zambon, Abbvie. *PV.* Consultant: Otsuka Pharmaceutical Europe. *SS.* Advisory Board: MSD, AbbVie; *MLS.* Lecture fees: Zambon; Advisory Board: Abbvie, Biogen Idec, Mundipharma, Pfizer, Takeda. *MV.* Advisory Board: Abbvie, Takeda, Hospira, Mundipharma, Pfizer, Biogen, Jannsen; Research grants: Sofar, Chiesi, MS&D, alfa-Wassermann; Lecture fee: MSD, Abbvie, Takeda, Chiesi Pfizer. *PV.* Consultant: Otsuka Pharmaceutical Europe.

References

[1] Summers RW, Switz DM, Sessions JT, et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology 1979;77:847–69.

[2] Malchow H, Ewe K, Brandes JW, et al. European Co-operative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology 1984;86:249–66.

[3] Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. British Medical Journal 1955;2:1041–8.

[4] Rosenberg W, Ireland A, Jewell DP. High-dose methylprednisolone in the treatment of active ulcerative colitis. Journal of Clinical Gastroenterology 1990;12:40–1.

[5] Bossa F, Fiorella S, Caruso N, et al. Continuous infusion versus bolus administration of steroids in severe attacks of ulcerative colitis: a randomized, double-blind trial. American Journal of Gastroenterology 2007;102:601–8.

[6] Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. Journal of Crohn's and Colitis 2010;4:28–62.

[7] Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's and Colitis 2012;6:991–1030.

[8] Tremaine WJ, Schroeder KW, Harrison JM, et al. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. Journal of Clinical Gastroenterology 1994;19:278–82.

[9] Singleton JW, Hanauer SB, Gitnick GL, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Gastroenterology 1993;104:1293–301.

[10] Cortot A, Colombel JF, Rutgeerts P. Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. Gut 2001;48:186–90.

[11] Sandborn WJ, Löfberg R, Feagan BG, et al. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. American Journal of Gastroenterology 2005;100: 1780–7.

[12] Campieri M, Adamo S, Valpiani D, et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Alimentary Pharmacology & Therapeutics 2003;17:1471–80.

[13] Sutherland LR, Singleton J, Sessions J, et al. Double-blind, placebo-controlled trial of metronidazole in Crohn's disease. Gut 1991;32:1071–5.

[14] Colombel JF, Lemann M, Cassagnou M, et al. A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. American Journal of Gastroenterology 1999;94:674–8.

[15] Prantera C, Zannoni F, Scribano ML, et al. An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. American Journal of Gastroenterology 1996;91:328–32.

[16] Candy S, Wright J, Gerber M, et al. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 1995;37:674–8.

[17] Lémann M, Mary JY, Colombel J-F, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology 2005;128:1812–8.

[18] Willoughby JM, Beckett J, Kumar PJ, et al. Controlled trial of azathioprine in Crohn's disease. Lancet 1971;ii:944–7.

[19] Rosenberg JL, Levin B, Wall AJ, et al. A controlled trial of azathioprine in Crohn's disease. American Journal of Digestive Diseases 1975;20:721–6.

[20] O'Donoghue DP, Dawson AM, Powell-Tuck J, et al. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. Lancet 1978;ii:955–7.

[21] Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. New England Journal of Medicine 2000;342:1627–32.

[22] D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120:1323–9.

[23] Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125:1025–31.

[24] van Dullemen HM, van Deventer SJ, Hommes DW, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology 1995;109:129–35.

[25] Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. New England Journal of Medicine 1997;337:1029–35.

[26] Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492–500.

[27] Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine 2005;353:2462–76.

[28] Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323–33.

[29] Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Annals of Internal Medicine 2007;146:829–38.

[30] Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257–65.

[31] Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85–95.

[32] Papamichael K, Van Stappen T, Jairath V, et al. Review article: pharmacological aspects of anti-TNF infliximab biosimilars in inflammatory bowel diseases. Alimentary Pharmacology & Therapeutics 2015;42:1158–69.

[33] Fiorino G, Girolomoni G, Lapadula G, et al. The use of biosimilars in immune-mediated disease: a joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. Autoimmunity Reviews 2014;13:751–5.

[34] Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine 2013;369(8):699–710.

[35] Bernstein CN, Fried M, Krabshuis JH, et al. World Gastroenterology Organization practice guidelines for the diagnosis and management of IBD in 2010. Inflammatory Bowel Diseases 2010;16:112–24.

[36] Orlando A, Armuzzi A, Papi C, et al. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: the use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. Digestive and Liver Disease 2011;43:1–20.

[37] OCEBM Levels of Evidence Working Group. The Oxford 2011 levels of evidence. Oxford Centre for Evidence-Based Medicine 2011; http://www.cebm.net/1433 index.aspx?o=5653.

[38] Svartz N. Salazypyrin, a new sulfanilamide preparation. A. Therapeutic results in rheumatic polyarthritis. B. Therapeutic results in ulcerative colitis. C. Toxic manifestations in treatment with sulfanilamide preparation. Acta Medica Scandinavica 1942;110:557–90.

[39] Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977;2:892–5.

[40] Loftus Jr EV, Kane SV, Bjorkman D. Systematic review: short term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. Alimentary Pharmacology & Therapeutics 2004;19:179–89.

[41] Feagan BG, MacDonald JK. Oral aminosalicylic acid for induction of remission 1444 in ulcerative colitis (Review). Cochrane Database of Systematic Review 2012;10. CD000544.

[42] Feagan BG, Chande N, MacDonald JK. Are there any differences in the efficacy and safety of different formulations of oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from Cochrane reviews. Inflammatory Bowel Diseases 2013;19:2031–40.

[43] Kamm MA, Sandborn WJ, Gassull M, et al. Once daily, high concentration MMX mesalamine in active ulcerative colitis. Gastroenterology 2007;132:66–75.

[44] Netzer P. Diffuse alopecia as side effect of mesalazine therapy in Crohn's disease. Schweizerische Medizinische Wochenschrift 1995;125:2438–42.

[45] Watkinson G. Sulphasalazine: a review of 40 years' experience. Drugs 1986;32(Suppl. 1):1–11.

[46] Poland GA, Love KR. Marked atypical lymphocytosis, hepatitis, and skin rash in sulfasalazine drug allergy. American Journal of Medicine 1986;81:707–8.

[47] Mihas AA, Goldenberg DJ, Slaughter RL. Sulfasalazine toxic reactions. Hepatitis, fever, and skin rash with hypocomplementemia and immune complexes. JAMA 1978;239:2590–1.

[48] Smith MD, Gibson GE, Rowland R. Combined hepatotoxicity and neurotoxicity following sulphasalazine administration. Australian and New Zealand Journal of Medicine 1982;12:76–80.

[49] Han T, Chawla PL, Sokal JE. Sulfapyridine-induced serum sickness-like syndrome associated with plasmacytosis, lymphocytosis and multiclonal gamma-globulinopathy. New England Journal of Medicine 1969;280:547–8.

[50] Tisdale WA. Focal hepatitis, fever and skin rash following therapy with sulfamethoxypyridazine, a long-acting sulfonamide. New England Journal of Medicine 1958;258:687–90.

[51] Faintuch J, Mott CB, Machado MC. Pancreatitis and pancreatic necrosis during sulfasalazine therapy. International Surgery 1985;70:271–2.

[52] Rubin R. Sulfasalazine-induced fulminant hepatic failure and necrotizing pancreatitis. American Journal of Gastroenterology 1994;89:789–91.

[53] Garau P, Orenstein SR, Neigut DA, et al. Pancreatitis associated with olsalazine and sulfasalazine in children with ulcerative colitis. Journal of Pediatric Gastroenterology and Nutrition 1994;18:481–5.

[54] Debongnie JC, Dekoninck X. Sulfasalazine, 5-ASA and acute pancreatitis in Crohn's disease. Journal of Clinical Gastroenterology 1994;19:348–9.

[55] Munk EM, Pedersen L, Floyd A, et al. Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. American Journal of Gastroenterology 2004;99:884–8.

[56] Lancashire RJ, Cheng K, Langman MJ. Discrepancies between population-based data and adverse reaction reports in assessing drugs as causes of acute pancreatitis. Alimentary Pharmacology & Therapeutics 2003;17:887–93.

[57] Douros A, Bronder E, Andersohn F, et al. Drug-induced acute pancreatitis: results from the hospital-based Berlin case-control surveillance study of 102 cases. Alimentary Pharmacology & Therapeutics 2013;38:825–34.

[58] Mallory A, Kern Jr F. Drug-induced pancreatitis: a critical review. Gastroenterology 1980;78:813–20.

[59] Block MB, Genant HK, Kirsner JB. Pancreatitis as an adverse reaction to salicylazosulfapyridine. New England Journal of Medicine 1970;282:380–2.

[60] Das KM, Eastwood MA, McManus JP, et al. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. New England Journal of Medicine 1973;289:491–5.

[61] Daneshmend TK. Mesalazine associated thrombocytopenia. Lancet 1991;337:1297–8.

[62] Casellas F, Vallano A, Malagelada JR. Leukopenia and thrombocytopenia as adverse effects of treatment with 5-aminosalicyclic suppositories. Journal of Clinical Gastroenterology 1996;22:160–1.

[63] Wyatt S, Joyner MV, Daneshmend TK. Filgastrim for mesalazine-associated neutropenia. Lancet 1993;341:1476.

[64] Turunen U, Elomaa I, Anthla VI, et al. Mesalazine tolerance in patients with inflammatory bowel disease and previous intolerance or allergy to sulphasalazine or sulphonamides. Scandinavian Journal of Gastroenterology 1987;22:798–802.

[65] Laidlaw ST, Reilly JT. Antilymphocyte globulin for mesalazine-associated aplastic anemia. Lancet 1994;343:981–2.

[66] Abboudi ZH, Marsh JC, Smith-Long G, et al. Fatal aplastic anemia after mesalazine. Lancet 1994;343:542 [letter].

[67] Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005;129:827–36.

[68] Ishikawa N, Imamura T, Nakajima K, et al. Acute pericarditis associated with 5-aminosalicylic acid (5-ASA) treatment for severe active ulcerative colitis. Internal Medicine 2001;40:901–4.

[69] Sentongo TA, Piccoli DA. Recurrent pericarditis due to mesalamine hypersensitivity: a pediatric case report and review of the literature. Journal of Pediatric Gastroenterology and Nutrition 1998;27:344–7.

[70] Perrot S, Aslangul E, Szwebel T, et al. Sulfasalazine-induced pericarditis in a patient with ulcerative colitis without recurrence when switching to mesalazine. International Journal of Colorectal Disease 2007;22:1119–21.

[71] Baker DE, Kane S. The short- and long-term safety of 5-aminosalicylate products in the treatment of ulcerative colitis. Reviews in Gastroenterological Disorders 2004;4:86–91.

[72] Di Paolo MC, Paoluzi OA, Pica R, et al. Sulphasalazine and 5-aminosalicylic acid in long-term treatment of ulcerative colitis: report on tolerance and side-effects. Digestive and Liver Disease 2001;33:563–9.

[73] Heap GA, So K, Weedon M, et al. Clinical features and HLA association of 5-aminosalicylate (5-ASA)-induced nephrotoxicity in inflammatory bowel disease. Journal of Crohn's and Colitis 2016;10:149–58.

[74] Muller AF, Stevens PE, McIntyre AS, et al. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. Alimentary Pharmacology & Therapeutics 2005;21:1217–24.

[75] Dehmer C, Greinwald R, Löffler J. No dose-dependent tubulotoxicity of 5-aminosalicylic acid: a prospective study in patients with inflammatory bowel diseases. International Journal of Colorectal Disease 2003;18:406–12.

[76] Elseviers MM, D'Haens G, Lerebours E, et al. Renal impairment in patients with inflammatory bowel disease: association with aminosalicylate therapy? Clinical Nephrology 2004;61:83–9.

[77] Travis SP, Stange EF, Lemann M, et al. European evidence-based consensus on the management of ulcerative colitis: current management. Journal of Crohn's and Colitis 2008;2:24–62.

[78] Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. American Journal of Gastroenterology 2010;105:501–23.

[79] Van Staa TP, Travis S, Leufkens HG, et al. 5-Aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. Gastroenterology 2004;126:1733–9.

[80] Corrigan G, Stevens PE. Review article: interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2000;14:1–6.

[81] World MJ, Stevens PE, Ashton MA, et al. Mesalazine associated interstitial nephritis. Nephrology Dialysis Transplantation 1996;11:614–21.

[82] Cunliffe RN, Scott BB. Review article: monitoring for drug side-effects in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2002;16:647–62.

[83] Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. Inflammatory Bowel Diseases 2007;13:629–38.

[84] Sannerstedt R, Lundborg P, Danielsson BR, et al. Drugs during pregnancy: an issue of risk classification and information to prescribers. Drug Safety 1996;14:69–77.

[85] Marteau P, Tennenbaum R, Elefant E, et al. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine micrograngules. Alimentary Pharmacology & Therapeutics 1998;12:1101–8.

[86] Diav-Citrin O, Park YH, Veerasuntharam G, et al. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. Gastroenterology 1998;114:23–8.

[87] Marteau P, Devaux CB. Mesalazine during pregnancy. Lancet 1994;344:1708–9.

[88] Sachar D. Exposure to mesalamine during pregnancy increased preterm deliveries (but not birth defects) and decreased birth weight. Gut 1998;43:316.

[89] Nørgård B, Fonager K, Pedersen L, et al. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. Gut 2003;52:243–7.

[90] Nørgård B, Pedersen L, Christensen LA, et al. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. American Journal of Gastroenterology 2007;102:1406–13.

[91] Ban L, Tata LJ, Fiaschi L, et al. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. Gastroenterology 2014;146:76–84.

[92] Marteau P, Seksik P, Couve S, et al. Safety of high doses of mesalazine during pregnancy. American Journal of Gastroenterology 2005;100:1897–8.

[93] Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. Reproductive Toxicology 2008;25:271–5.

[94] Moffatt DC, Bernstein CN. Drug therapy for inflammatory bowel disease in pregnancy and the puerperium. Best Practice & Research Clinical Gastroenterology 2007;21:835–47.

[95] Position paper Agenzia Italiana per il Farmaco (AIFA), 2013.

[96] Peppa M, Krania M, Raptis SA. Hypertension and other morbidities with Cushing's syndrome associated with corticosteroids: a review. Integrated Blood Pressure Control 2011;4:7–16.

[97] Whitworth JA, Williamson PM, Mangos G, et al. Cardiovascular consequences of cortisol excess. Vascular Health and Risk Management 2005;1:291–9.

[98] Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Annals of the Rheumatic Diseases 2006;65:285–93.

[99] Sherlock ME, Seow CH, Steinhart AH, et al. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2010:CD007698.

[100] Toruner M, Loftus Jr EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008;134:929–36.

[101] Rahier JF, Magrob F, Abreue C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis 2014;8:443–68.

[102] van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporosis International 2002;13:777–87.

[103] Ström O, Borgström F, Kanis JA, et al. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of Osteoporosis 2011;6:59–155.

[104] Hauzeur J, Malaise M, Gangji V. Osteonecrosis in inflammatory bowel diseases: a review of the literature. Acta Gastro-Enterologica Belgica 2009;72:327–34.

[105] Subramanian V, Saxena S, Kang JY, et al. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. American Journal of Gastroenterology 2008;103:2373–81.

[106] Aberra FN, Lewis JD, Hass D, et al. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology 2003;125:320–7.

[107] Ferrante M, D'Hoore A, Vermeire S, et al. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. Inflammatory Bowel Disease 2009;15:1062–70.

[108] van der Woude CJ, Sanja Kolacek S, Dotan I, et al. European evidenced-based consensus on reproduction in inflammatory bowel disease. Journal of Crohn's and Colitis 2010;4:493–510.

[109] Bortoli A, Pedersen N, Duricova D, et al. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003–2006. Alimentary Pharmacology & Therapeutics 2011;34:724–34.

[110] Day AC, Baio G, Gazzard G, et al. The prevalence of primary angle closure glaucoma in European derived populations: a systematic review. British Journal of Ophthalmology 2012;96:1162–7.

[111] Oray M, Abu Samra K, Ebrahimiadib N, et al. Long-term side effects of glucocorticoids. Expert Opinion on Drug Safety 2016;15:457–65.

[112] Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clinical Gastroenterology and Hepatology 2006;4:621–30.

[113] Fascì Spurio F, Aratari A, Margagnoni G, et al. Low bioavailability and traditional systemic steroids in IBD: can the former take over the latter? Journal of Gastrointestinal and Liver Diseases 2013;22:65–71.

[114] D'Haens GR, Kovács A, Vergauwe P, et al. Clinical trial: preliminary efficacy and safety study of a new Budesonide-MMX® 9 mg extended-release tablets in patients with active left-sided ulcerative colitis. Journal of Crohn's and Colitis 2010;4:153–60.

[115] Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. New England Journal of Medicine 1994;331:836–41.

[116] Tremaine WJ, Hanauer SB, Katz S, et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. American Journal of Gastroenterology 2002;97:1748–54.

[117] Tromm A, Bunganič I, Tomsová E, et al. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. Gastroenterology 2011;140:425–34, e1.

[118] Thomsen OO, Cortot A, Jewell D, et al. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. New England Journal of Medicine 1998;339:370–4 [Erratum in: New England Journal of Medicine 2001;345:1652].

[119] Rutgeerts P, Löfberg R, Malchow H, et al. A comparison of budesonide with prednisolone for active Crohn's disease. New England Journal of Medicine 1994;331:842–5.

[120] Gross V, Andus T, Caesar I, et al. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. German/Austrian Budesonide Study Group. European Journal of Gastroenterology & Hepatology 1996;8:905–9.

[121] Campieri M, Ferguson A, Doe W, et al. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut 1997;41:209–14.

[122] Bar-Meir S, Chowers Y, Lavy A, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. Gastroenterology 1998;115:835–40.

[123] Escher JC, European Collaborative Research Group on Budesonide in Paediatric IBD. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. European Journal of Gastroenterology & Hepatology 2004;16:47–54.

[124] Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology 2012;143:1218–26.

[125] Travis SP, Danese S, Kupcinskas L, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut 2014;63:433–41.

[126] Gross V, Bunganic I, Belousova EA, et al. 3 g mesalazine granules are superior to 9 mg budesonide for achieving remission in active ulcerative colitis: a double-blind, double-dummy, randomised trial. Journal of Crohn's and Colitis 2011;5:129–38.

[127] Löfberg R, Danielsson A, Suhr O, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. Gastroenterology 1996;110:1713–8.

[128] Lichtenstein GR, Travis S, Danese S, et al. Budesonide MMX for the induction of remission of mild to moderate ulcerative colitis: a pooled safety analysis. Journal of Crohn's and Colitis 2015;9:738–46.

[129] Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. American Journal of Gastroenterology 2011;106:590–9.

[130] Rizzello F, Gionchetti P, D'Arienzo A, et al. Oral beclomethasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. Alimentary Pharmacology & Therapeutics 2002;16:1109–16.

[131] Van Assche G, Manguso F, Zibellini M, et al. Oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, Parallel Group Study. American Journal of Gastroenterology 2015;110:708–15.

[132] Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. Gastroenterology 1996;110:45–51.

[133] Löfberg R, Rutgeerts P, Malchow H, et al. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. Gut 1996;39:82–6.

[134] Gross V, Andus T, Ecker KW, et al. Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. Gut 1998;42:493–6.

[135] Hanauer S, Sandborn WJ, Persson A, et al. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. Alimentary Pharmacology & Therapeutics 2005;21:363–71.

[136] Kuenzig ME, Rezaie A, Seow CH, et al. Budesonide for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2014;21:CD002913.

[137] Hellers G, Cortot A, Jewell D, et al. Oral budesonide for prevention of post-surgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. Gastroenterology 1999;116:294–300.

[138] Ewe K, Böttger T, Buhr HJ, et al. Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. European Journal of Gastroenterology & Hepatology 1999;11:277–82.

[139] Schoon EJ, Bollani S, Mills PR, et al. Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in Crohn's disease. Clinical Gastroenterology and Hepatology 2005;3:113–21.

[140] Prantera C, Rizzi M, Cottone M, et al. Beclomethasone dipropionate in Crohn's ileitis: a randomised, double-blind trial. Digestive and Liver Disease 2011;43:459–64.

[141] D'Haens G, Verstraete A, Cheyns K, et al. Bone turnover during short-term therapy with methylprednisolone or budesonide in Crohn's disease. Alimentary Pharmacology & Therapeutics 1998;12:419–24.

[142] Cino M, Greenberg GR. Bone mineral density in Crohn's disease: a longitudinal study of budesonide, prednisone, and nonsteroid therapy. American Journal of Gastroenterology 2002;97:915–21.

[143] Lichtenstein GR, Bengtsson B, Hapten-White L, et al. Oral budesonide for maintenance of remission of Crohn's disease: a pooled safety analysis. Alimentary Pharmacology & Therapeutics 2009;15:643–53.

[144] Beaulieu DB, Ananthakrishnan AN, Issa M, et al. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. Inflammatory Bowel Diseases 2009;15:25–8.

[145] Christensson C, Thorén A, Lindberg B. Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. Drug Safety 2008;31:965–88.

[146] de Aguiar MM, da Silva HJ, Rizzo JA, et al. Inhaled beclomethasone in pregnant asthmatic women—a systematic review. Allergologia et Immunopathologia 2014;42:493–9.

[147] Powrie RO, Larson L, Miller M. Managing asthma in expectant mothers. Treatments in Respiratory Medicine 2006;5:1–10.

[148] Nielsen OH, Maxwell C, Hendel J. IBD medications during pregnancy and lactation. Nature Reviews Gastroenterology & Hepatology 2014;11:116–27.

[149] Gionchetti P, Dignass A, Magro FD, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. Journal of Crohn's Colitis 2016;11:135–49.

[150] Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis: special situations. Journal of Crohn's and Colitis 2013;7:1–33.

[151] Segev S, Yaniv I, Haverstock D, et al. Safety of long-term therapy with ciprofloxacin: data analysis of controlled clinical trials and review. Clinical Infectious Diseases 1999;28:299–308.

[152] Owens R, Ambrose P. Antimicrobial safety: focus on fluoroquinolones. Clinical Infectious Diseases 2005;41(Suppl. 2):S144–57.

[153] Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. Clinical Gastroenterology and Hepatology 2007;5:345–51.

[154] Orman ES, Conjeevaram HS, Vuppalanchi R, et al. Clinical and histopathological features of fluoroquinolone-induced liver injury. Clinical Gastroenterology and Hepatology 2011;9:517–23.

[155] Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Safety 2011;34:465–88.

[156] Melhus A. Fluoroquinolones and tendon disorders. Expert Opinion on Drug Safety 2005;4:299–309.

[157] Adefurin A, Sammons H, Jacqz-Aigrain E, et al. Ciprofloxacin safety in paediatrics: a systematic review. Archives of Disease in Childhood 2011;96:874–80.

[158] Van der Linden PD, Sturkenboom MC, Herings RM, et al. Fluoroquinolones and risk of achilles tendon disorders: case-control study. BMJ 2002;324:1306–7.

[159] Arabyat RM, Raisch DW, McKoy JM, et al. Fluoroquinolone-associated tendon-rupture: a summary of reports in the Food and Drug Administration's adverse event reporting system. Expert Opinion on Drug Safety 2015;14:1653–60.

[160] Prabhakar M, Khran AD. Ciprofloxacin-induced acquired long QT syndrome. Heart Rhythm 2004;1:624–6.

[161] Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617–21.

[162] Karamanakos PN, Pappas P, Boumba VA, et al. Pharmaceutical agents known to produce disulfiram-like reaction: effects on hepatic ethanol metabolism and brain monoamines. International Journal of Toxicology 2007;26:423–32.

[163] Smith JA. Neutropenia associated with metronidazole therapy. Canadian Medical Association Journal 1980;123:202.

[164] Kuriyama A, Jackson JL, Doi A, et al. Metronidazole-induced central nervous system toxicity: a systematic review. Clinical Neuropharmacology 2011;34:241–7.

[165] Bernstein LH, Frank MS, Brandt LJ, et al. Healing of perianal Crohn's disease with metronidazole. Gastroenterology 1980;79:357–65.

[166] Jacobovits J, Schuster MM. Metronidazole therapy for Crohn's disease and associated fistulae. American Journal of Gastroenterology 1984;79:533–40.

[167] Gillis JC, Brogden RN. Rifaximin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic potential in conditions mediated by gastrointestinal bacteria. Drugs 1995;49:467–84.

[168] Scarpignato C, Pelosini I. Rifaximin, a poorly absorbed antibiotic: pharmacology and clinical potential. Chemotherapy 2005;51(Suppl. 1):36–66.

[169] Berkovitch M, Pastuszak A, Gazarian M, et al. Safety of the new quinolones in pregnancy. Obstetrics & Gynecology 1994;84:535–8.

[170] Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrobial Agents and Chemotherapy 1998;42:1336–9.

[171] van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. Journal of Crohn's and Colitis 2015;9:107–24.

[172] Mahadevan U, Kane S. American Gastroenterological Association institute technical review on the use of gastrointestinal medications in pregnancy. Gastroenterology 2006;131:283–311.

[173] Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. British Journal of Obstetrics and Gynaecology 1998;105:322–7.

[174] Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. American Journal of Obstetrics & Gynecology 1995;172:525–9.

[175] Caro-Paton T, Carvajal A, Martin de Diego I, et al. Is metronidazole teratogenic? A meta-analysis. British Journal of Clinical Pharmacology 1997;44:179–82.

[176] Koss CA, Baras DC, Lane SD, et al. Investigation of metronidazole use during pregnancy and adverse birth outcomes. Antimicrobial Agents and Chemotherapy 2012;56:4800–5.

[177] Mathew JL. Effect of maternal antibiotics on breast feeding infants. Postgraduate Medical Journal 2004;80:196–200.

[178] Chaparro M. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. Inflammatory Bowel Diseases 2013;19:1404–10.

[179] Saibeni S, Virgilio T, D'Incà R, et al. The use of thiopurines for the treatment of inflammatory bowel diseases in clinical practice. Digestive and Liver Disease 2008;40:814–20.

[180] Jharap B, Seinen ML, de Boer NK, et al. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. Inflammatory Bowel Diseases 2010;16:1541–9.

[181] Costantino G, Furfaro F, Belvedere A, et al. Thiopurine treatment in inflammatory bowel disease: response predictors, safety, and withdrawal in follow-up. Journal of Crohn's and Colitis 2012;6:588–96.

[182] Kim PS, Zlatanic J, Korelitz BI, et al. Optimum duration of treatment with 6-mercaptopurine for Crohn's disease. American Journal of Gastroenterology 1999;94:3254–7.

[183] Bidinger JJ, Sky K, Battafarano DF, et al. The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome. Journal of the American Academy of Dermatology 2011;65:184–91.

[184] Lewis JD, Abramson O, Pascua M, et al. Timing of myelosuppression during thiopurine therapy for inflammatory bowel disease: implications for monitoring recommendations. Clinical Gastroenterology and Hepatology 2009;7:1195–201.

[185] Gisbert JP, Gomollón F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. American Journal of Gastroenterology 2008;103:1783–800.

[186] Lennard L. The clinical pharmacology of 6-mercaptopurine. European Journal of Clinical Pharmacology 1992;43:329–39.

[187] Dubinsky MC, Yang H, Hassard PV, et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. Gastroenterology 2002;122:904–15.

[188] Lennard L, Lilleyman JS, Van Loon J, et al. Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukemia. Lancet 1990;336:225–9.

[189] Gisbert JP, Niño P, Rodrigo L, et al. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. American Journal of Gastroenterology 2006;101:2769–76.

[190] Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology 2000;118:705–13.

[191] Cuffari C, Theorêt Y, Latour S, et al. 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. Gut 1996;39:401–6.

[192] Roblin X, Peyrin-Biroulet L, Phelip JM, et al. A 6-thioguanine nucleotide threshold level of $400\,pmol/8 \times 10(8)$ erythrocytes predicts azathioprine refractoriness in patients with inflammatory bowel disease and normal TPMT activity. American Journal of Gastroenterology 2008;103:3115–22.

[193] Dubinsky MC, Reyes E, Ofman J, et al. A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. American Journal of Gastroenterology 2005;100:2239–47.

[194] Gisbert JP, Niño P, Rodrigo L, et al. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. American Journal of Gastroenterology 2006;101:2769–76.

[195] Relling MV, Gardner EE, Sandborn WJ, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase

genotype and thiopurine dosing. Clinical Pharmacology & Therapeutics 2011;89:387–91.

[196] Zur RM, Roy LM, Ito S, et al. Thiopurine S-methyltransferase testing for averting drug toxicity: a meta-analysis of diagnostic test accuracy. Pharmacogenomics Journals 2016;17:633–56.

[197] Palmieri O, Latiano A, Bossa F, et al. Sequential evaluation of thiopurine methyltransferase, inosine triphosphate pyrophosphatase, and HPRT1 genes polymorphisms to explain thiopurines' toxicity and efficacy. Alimentary Pharmacology & Therapeutics 2007;26:737–45.

[198] Winter J, Walker A, Shapiro D, et al. Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2004;20:593–9.

[199] Van den Akkervan Marle ME, Gurwitz D, Detmar SB, et al. Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lymphoblastic leukaemia in Europe. Pharmacogenomics 2006;7:783–92.

[200] Compagni A, Bartoli S, Buehrlen B, et al. Avoiding adverse drug reactions by pharmacogenetic testing: a systematic review of the economic evidence in the case of TPMT and AZA-induced side effects. International Journal of Technology Assessment in Health Care 2008;24:294–302.

[201] Priest VL, Begg EJ, Gardiner SJ, et al. Pharmacoeconomic analyses of azathioprine methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. Pharmacoeconomics 2006;24:761–81.

[202] Sayani FA, Prosser C, Bailey RJ, et al. Thiopurine methyltransferase enzyme activity determination before treatment of inflammatory bowel disease with azathioprine: effect on cost and adverse events. Canadian Journal of Gastroenterology 2005;19:147–51.

[203] Bermejo F, López-Sanromán A, Algaba A, et al. Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2010;31:120–4.

[204] Kiefer K, El-Matary W. 6-Mercaptopurine as an alternative to azathioprine in azathioprine-induced hepatoxicity. Inflammatory Bowel Diseases 2009;15:318–9.

[205] Kennedy NA, Rhatigan E, ArnoltI D, et al. A trial of mercaptopurine is a safe strategy in patients with inflammatory bowel disease intolerant to azathioprine: an observational study, systematic review and meta-analysis. Alimentary Pharmacology & Therapeutics 2013;38:1255–66.

[206] Tuyama AC, Karakauer M, Alzaabi M, et al. Mercaptopurine induced hepatoportal sclerosis in a patient with Crohn's Disease. Journal of Crohn's and Colitis 2013;7:590–3.

[207] Konidari A, Matary WE. Use of thiopurines in inflammatory bowel disease: safety issues. World Journal of Gastrointestinal Pharmacology and Therapeutics 2014;5:63–76.

[208] Sansone S, Guarino M, Castiglione F, et al. Hepatitis B and C virus reactivation in immunosuppressed patients with inflammatory bowel disease. World Journal of Gastroenterology 2014;20:3516–24.

[209] Dewit O, Vanheuverzwyn R, Desager JP, et al. Interaction between azathioprine and aminosalicylates: an in vivo study in patients with Crohn's disease. Alimentary Pharmacology & Therapeutics 2002;16:79–85.

[210] Daperno M, Sostegni R, Canaparo R, et al. Prospective study of the effects of concomitant medications on thiopurine metabolism in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2009;30:843–53.

[211] Ansari A, Patel N, Sanderson J, et al. Low-dose azathioprine or mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2010;31:640–7.

[212] Govani SM, Higgins PD. Combination of thiopurines and allopurinol: adverse events and clinical benefit in IBD. Journal of Crohn's and Colitis 2010;4:444–9.

[213] Vögelin M, Biedermann L, Frei P, et al. The impact of azathioprine-associated lymphopenia on the onset of opportunistic infections in patients with inflammatory bowel disease. PLoS One 2016;11:e0155218.

[214] Teksik P, Cosnes J, Sokol H, et al. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. Alimentary Pharmacology & Therapeutics 2009;29:1106–13.

[215] James DG, Stone CD, Wang HL, et al. Reactive hemophagocytic syndrome complicating the treatment of inflammatory bowel disease. Inflammatory Bowel Diseases 2006;12:573–80.

[216] Connell WR, Kamm MA, Dickson M, et al. Long-term neoplasia risk after azathioprine treatment in Inflammatory Bowel Disease. Lancet 1994;343:1249–52.

[217] Glick SN, Teplick SK, Goodman LR, et al. Development of lymphoma in patients with Crohn's disease. Radiology 1984;153:337–9.

[218] Khan N, Abbas AM, Lichtenstein GR, et al. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. Gastroenterology 2013;145:1007–15.

[219] Lakatos PL, Lovasz BD, David G, et al. The risk of lymphoma and immunomodulators in patients with inflammatory bowel diseases: results from a population-based cohort in Eastern Europe. Journal of Crohn's and Colitis 2013;7:385–91.

[220] Lewis J, Schwartz S, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. Gastroenterology 2000;118:1018–24.

[221] Dayharsh G, Loftus EV, Sandborn WJ, et al. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine. Gastroenterology 2002;122:72–7.

[222] Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54:1121–5.

[223] Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009;374:1617–25.

[224] Vos AC, Bakkal N, Minnee RC, et al. Risk of malignant lymphoma in patients with inflammatory bowel diseases: a Dutch nationwide study. Inflammatory Bowel Diseases 2011;17:1837–45.

[225] Long MD, Herfarth HH, Pipkin CA, et al. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. Clinical Gastroenterology and Hepatology 2010;8:268–74.

[226] Setshedi M, Epstein D, Winter TA, et al. Use of thiopurines in the treatment of inflammatory bowel disease is associated with an increased risk of non-melanoma skin cancer in an at-risk population: a cohort study. Journal of Gastroenterology and Hepatology 2012;27:385–9.

[227] Long MD, Kappelman MD, Pipkin CA. Nonmelanoma skin cancer in inflammatory bowel disease: a review. Inflammatory Bowel Diseases 2011;17:1423–7.

[228] Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for non-melanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology 2011;141:1621–8.

[229] Ariyaratnam J, Subramanian V. Association between thiopurine use and non-melanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. American Journal of Gastroenterology 2014;109:163–9.

[230] Bourrier A, Carrat F, Colombel JF, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Alimentary Pharmacology & Therapeutics 2016;43:252–61.

[231] Colombel JF, Loftus Jr EV, Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. American Journal of Gastroenterology 2004;99:878–83.

[232] Mahadevan U, Loftus Jr EV, Tremaine WJ, et al. Azathioprine or 6-mercaptopurine before colectomy for ulcerative colitis is not associated with increased postoperative complications. Inflammatory Bowel Diseases 2002;8:311–6.

[233] Damas OM, Deshpande AR, Avalos DJ, et al. Treating inflammatory bowel disease in pregnancy: the issues we face today. Journal of Crohn's and Colitis 2015;9:928–36.

[234] Kwan LY, Mahadevan U. Inflammatory bowel disease and pregnancy: an update. Expert Review of Clinical Immunology 2010;6:643–57.

[235] Casanova MJ, Chaparro M, Domènech E, et al. Safety of thiopurines and anti-TNF-á drugs during pregnancy in patients with inflammatory bowel disease. American Journal of Gastroenterology 2013;108:433–40.

[236] Caprilli R, Angelucci E, Cocco A, et al. Appropriateness of immunosuppressive drugs in inflammatory bowel diseases assessed by RAND method: Italian Group for IBD (IG-IBD) position statement. Digestive and Liver Disease 2005;37:407–17.

[237] Jharap B, de Boer NK, Stokkers P, et al. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. Gut 2014;63:451–7.

[238] Teruel C, López-San Román A, Bermejo F, et al. Outcomes of pregnancies fathered by inflammatory bowel disease patients exposed to thiopurines. American Journal of Gastroenterology 2010;105:2003–8.

[239] Rajapakse RO, Korelitz BI, Zlatanic J, et al. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. American Journal of Gastroenterology 2000;95:648–84.

[240] Akbari M, Shah S, Velayos FS, et al. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. Inflammatory Bowel Diseases 2013;19:15–22.

[241] Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. The New England Journal of Medicine 1995;332:292–7.

[242] Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2013;5:CD000951.

[243] Malatjalian DA, Ross JB, Williams CN, et al. Methotrexate hepatotoxicity in psoriatics: report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. Canadian Journal of Gastroenterology 1996;10:369–75.

[244] Lewis JH, Schiff E. Methotrexate-induced chronic liver injury: guidelines for detection and prevention. The ACG Committee on FDA-related matters. American College of Gastroenterology. American Journal of Gastroenterology 1988;83:1337–45.

[245] Suares NC, Hamlin PJ, Greer DP, et al. Efficacy and tolerability of methotrexate therapy for refractory Crohn's disease: a large single-centre experience. Alimentary Pharmacology & Therapeutics 2012;35:284–91.

[246] Cummings JR, Herrlinger KR, Travis SP, et al. Oral methotrexate in ulcerative colitis. Alimentary Pharmacology & Therapeutics 2005;21:385–9.

[247] Chande N, Abdelgadir I, Gregor J. The safety and tolerability of methotrexate for treating patients with Crohn's disease. Journal of Clinical Gastroenterology 2011;45:599–601.

[248] Khan N, Abbas AM, Whang N, et al. Incidence of liver toxicity in inflammatory bowel disease patients treated with methotrexate: a meta-analysis of clinical trials. Inflammatory Bowel Diseases 2012;18:359–67.

[249] Lemann M, Zenjari T, Bouhnik Y, et al. Methotrexate in Crohn's disease: long-term efficacy and toxicity. American Journal of Gastroenterology 2000;95:1730–4.

[250] Te HS, Schiano TD, Kuan SF, et al. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. American Journal of Gastroenterology 2000;95:3150–6.

[251] Watanabe K, Takase K, Ohno S, et al. Reactivation of hepatitis B virus in a hepatitis B surface antigen-negative patient with rheumatoid arthritis treated with methotrexate. Modern Rheumatology 2012;22:470–3.

[252] Barbero-Villares A, Mendoza Jimenez-Ridruejo J, Taxonera C, et al. Evaluation of liver fibrosis by transient elastography (Fibroscan(R)) in patients with inflammatory bowel disease treated with methotrexate: a multicentric trial. Scandinavian Journal of Gastroenterology 2012;47:575–9.

[253] Kremer JM, Alarcon GS, Lightfoot Jr RW, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis & Rheumatology 1994;37:316–28.

[254] Powell HR, Ekert H. Methotrexate-induced congenital malformations. Medical Journal of Australia 1971;2:1076–7.

[255] Saibeni S, Bollani S, Losco A, et al. The use of methotrexate for treatment of inflammatory bowel disease in clinical practice. Digestive and Liver Disease 2012;44:123–7.

[256] Sandborn WJ. A critical review of cyclosporine therapy in inflammatory bowel disease. Inflammatory Bowel Diseases 1995;1:48–63.

[257] Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. New England Journal of Medicine 1994;330:1841–5.

[258] Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis 2009;3:47–91.

[259] Campbell S, Travis S, Jewell D. Cyclosporin use in acute ulcerative colitis: a long-term experience. European Journal of Gastroenterology & Hepatology 2005;17:79–84.

[260] Dantal J, Pohanka E. Malignancies in renal transplantation: an unmet medical need. Nephrology Dialysis Transplantation 2007;22(Suppl. 1):i4–10.

[261] Muellenhoff MW, Koo JY. Cyclosporine and skin cancer: an international dermatologic perspective over 25 years of experience. A comprehensive review and pursuit to define safe use of cyclosporine in dermatology. Journal of Dermatological Treatment 2012;23:290–304.

[262] Beyaert R, Beaugerie L, Van Assche G, et al. Cancer risk in immune-mediated inflammatory diseases (IMID). Molecular Cancer 2013;12:98.

[263] Masunaga Y, Ohno K, Ogawa R, et al. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. Annals of Pharmacotherapy 2007;41:21–8.

[264] Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. New England Journal of Medicine 2003;348:1681–91.

[265] Moloney FJ, Comber H, O'Lorcain P, et al. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. British Journal of Dermatology 2006;154:498–504.

[266] Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomized comparison of two cyclosporin regimens. Lancet 1998;351:623–8.

[267] Hyde GM, Jewell DP, Kettlewell MG, et al. Cyclosporin for severe ulcerative colitis does not increase the rate of perioperative complications. Diseases of the Colon & Rectum 2001;44:1436–40.

[268] Poritz LS, Rowe WA, Swenson BR, et al. Intravenous cyclosporine for the treatment of severe steroid refractory ulcerative colitis: what is the cost? Diseases of the Colon & Rectum 2005;48:1685–90.

[269] Costa ML, Surita FG, Passini R, et al. Pregnancy outcome in female liver transplant recipients. Transplant Immunology 2011;43:1337–9.

[270] Millsop JW, Heller MM, Eliason MJ, et al. Dermatological medication effects on male fertility. Dermatologic Therapy 2013;26:337–46.

[271] Gisbert JP. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. Inflammatory Bowel Diseases 2010;16:881–95.

[272] Perales-Puchalt A, Vila Vives JM, Lopez Montes J, et al. Pregnancy outcomes after kidney transplantation—immunosuppressive therapy comparison. Maternal-Fetal and Neonatal Medicine 2012;25:1363–6.

[273] Branche J, Cortot A, Bourreille A, et al. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. Inflammatory Bowel Diseases 2009;15:1044–8.

[274] Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-related infusion reactions: systematic review. Journal of Crohn's and Colitis 2015;9:806–15.

[275] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–9.

[276] Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. New England Journal of Medicine 2004;350:876–85.

[277] Colombel JF, Loftus Jr EV, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126:19–31.

[278] Lees CW, Ali AI, Thompson AI, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis

[279] Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. American Journal of Gastroenterology 2003;98:1315–24.

[280] Fidder H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single centre cohort study. Gut 2009;58:501–8.

[281] Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clinical Gastroenterology and Hepatology 2004;2:542–53.

[282] Steenholdt C, Svenson M, Bendtzen K, et al. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2011;34:51–8.

[283] Kugathasan S, Levy MB, Saeian K, et al. Infliximab retreatment in adults and children with Crohn's disease: risk factors for the development of delayed severe systemic reaction. American Journal of Gastroenterology 2002;97:1408–14.

[284] Narula N, Kainz S, Petritsch W, et al. The efficacy and safety of either infliximab or adalimumab in 362 patients with anti-TNF-α naïve Crohn's disease. Alimentary Pharmacology & Therapeutics 2016;44:170–80.

[285] Magro F, Marques M, Santos CC. Episodic infliximab treatment induces infusion reactions. Inflammatory Bowel Diseases 2008;14:1608–10.

[286] Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–13.

[287] O'Meara S, Nanda KS, Moss AC. Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflammatory Bowel Diseases 2014;20:1–6.

[288] Ainsworth MA, Bendtzen K, Brynskov J. Tumor necrosis factor-alpha binding capacity and anti-Infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of Infliximab in Crohn's disease. American Journal of Gastroenterology 2008;103:944–8.

[289] Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. Inflammatory Bowel Diseases 2009;15:1264–75.

[290] Maggi E, Vultaggio A, Matucci A. Acute infusion reactions induced by monoclonal antibody therapy. Expert Review of Clinical Immunology 2011;7:55–63.

[291] Ben-Horin S, Mazor Y, Yanai H, et al. The decline of anti-drug antibody titres after discontinuation of anti-TNFs: implications for predicting re-induction outcome in IBD. Alimentary Pharmacology & Therapeutics 2012;35:714–22.

[292] Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut 2007;56:1226–31.

[293] Neef HC, Riebschleger MP, Adler J. Meta-analysis: rapid infliximab infusions are safe. Alimentary Pharmacology & Therapeutics 2013;38:365–76.

[294] Farrell RJ, Alsahli M, Jeen YT, et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 2003;124:917–24.

[295] Jacobstein DA, Markowitz JE, Kirschner BS, et al. Premedication and infusion reactions with infliximab: results from a pediatric inflammatory bowel disease consortium. Inflammatory Bowel Diseases 2005;11:442–6.

[296] Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232–9.

[297] Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.

[298] Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85–95.

[299] Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:96–109.

[300] Mounach A, Rezqi A, Nouijai A, et al. Stevens–Johnson syndrome complicating adalimumab therapy in rheumatoid arthritis disease. Rheumatology International 2013;33:1351–3.

[301] Marques I, Lagos A, Reis J, et al. Reversible Henoch–Schönlein purpura complicating adalimumab therapy. Journal of Crohn's and Colitis 2012;6:796–9.

[302] Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clinical Gastroenterology and Hepatology 2016;14(10):1385–97.

[303] Danese S, Gomollon F, Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). Journal of Crohn's and Colitis 2013;7:586–9.

[304] Danese S, Fiorino G, Michetti P. Changes in biosimilar knowledge among European Crohn's Colitis Organization (ECCO) members: a updated survey. Journal of Crohn's and Colitis 2016;10(11):1362–5.

[305] Gecse KB, Khanna R, van den Brink GR, et al. Biosimilars in IBD: hope or expectation? Gut 2013;62:803–7.

[306] AIFA. Position paper su farmaci biosimilari. http://www.agenziafarmaco. gov. 2228 it/it/content/position-paper-sui-farmaci-biosimilari-28052013 [Accessed 28 2229 May 2013]. 2230; 2013.

[307] Annese V, Vecchi M. Statements of the Italian Group for inflammatory bowel disease. Digestive and Liver Disease 2014;46:963–8.

[308] Fiorino G, Manetti N, Armuzzi A, et al. The PROSIT-BIO cohort: a prospective observational study of patients with inflammatory bowel disease treated with infliximab biosimilar. Inflammatory Bowel Diseases 2017;23:233–43, http://dx.doi.org/10.1097/MIB.000000000000099.

[309] Scott FI, Lichtenstein GR. Therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease. Current Treatment Options in Gastroenterology 2014;12:59–75.

[310] Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. New England Journal of Medicine 2003;348:601–8.

[311] Kerbleski JF, Gottlieb AB. Dermatological complications and safety of anti-TNF treatments. Gut 2009;58:1033–9.

[312] Schaible TF. Long term safety of infliximab. Canadian Journal of Gastroenterology 2000;14(Suppl. C):29C–32C.

[313] Ramos-Casals M, Brito-Zerón P, Soto MJ, et al. Autoimmune diseases induced by TNF-targeted therapies. Best Practice & Research Clinical Rheumatology 2008;22:847–51.

[314] Yates VM, Watkinson G, Kelman A. Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. British Journal of Dermatology 1982;106:323–30.

[315] Ellinghaus D, Ellinghaus E, Nair RP, et al. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. American Journal of Human Genetics 2012;90:636–47.

[316] Cullen G, Kroshinsky D, Cheifetz AS, et al. Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: a new series and a review of 120 cases from the literature. Alimentary Pharmacology & Therapeutics 2011;34:1318–27.

[317] Afzal A, Wheat CL, Hu JK, et al. The association of psoriasiform rash with anti-tumor necrosis factor (anti-TNF) therapy in inflammatory bowel disease: a single academic center case series. Journal of Crohn's and Colitis 2014;8:480–8.

[318] Guerra I, Algaba A, Pérez-Calle JL, et al. Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: a report of 21 cases. Journal of Crohn's and Colitis 2012;6:518–23.

[319] Cleynen I, Moerkercke WV, Billiet T, et al. Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: a cohort study. Annals of Internal Medicine 2016;164:10–22.

[320] Fréling E, Baumann C, Cuny JF, et al. Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience. American Journal of Gastroenterology 2015;110:1186–96.

[321] Passarini B, Infusino SD, Barbieri E, et al. Cutaneous manifestations in inflammatory bowel diseases: eight cases of psoriasis induced by anti-tumor-necrosis-factor antibody therapy. Dermatology 2007;215:295–300.

[322] Mocci G, Marzo M, Papa A, et al. Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. Journal of Crohn's and Colitis 2013;7:769–79.

[323] Pugliese D, Guidi L, Ferraro PM, et al. Paradoxical psoriasis in a large cohort of patients with inflammatory bowel disease receiving treatment with anti-TNF alpha: 5-year follow-up study. Alimentary Pharmacology & Therapeutics 2015;42:880–8.

[324] Harrison MCJ, Dixon WG, Watson KD, et al. BSRBR rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Annals of the Rheumatic Diseases 2009;68:209–15.

[325] Baeten D, Kruithof E, Van den Bosch F, et al. Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? Rheumatic Diseases 2003;62:829–34.

[326] Niess JH, Danese S. Anti-TNF and skin inflammation in IBD: a new paradox in gastroenterology? Gut 2014;63:533–5.

[327] Afzali A, Wheat CL, Hu JK, et al. The association of psoriasiform rash with anti-tumor necrosis factor (anti-TNF) therapy in inflammatory bowel disease: a single academic center case series. Journal of Crohn's and Colitis 2014;8:480–8.

[328] Tillack C, Ehmann LM, Friedrich M, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17 A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. Gut 2014;63:567–77.

[329] Moran GW, Lim AW, Bailey JL, et al. Review article: dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2013;38:1002–24.

[330] Perdan-Pirkmajer K, Hočevar A, Rotar Ž, et al. Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry. Rheumatology International 2013;33:2885–9.

[331] Rowe BW, Gala-Lopez B, Tomlinson C, et al. Fulminant hepatic failure necessitating transplantation following the initiation of infliximab therapy: a cautionary tale times two. Transplant International 2013;26:e110–2.

[332] Di Minno MN, Iervolino S, Peluso R, et al. Hepatic steatosis and disease activity in subjects with psoriatic arthritis receiving tumor necrosis factor-α blockers. Journal of Rheumatology 2012;39:1042–6.

[333] Poulin Y, Thérien G. Drug-induced hepatitis and lupus during infliximab treatment for psoriasis: case report and literature review. Journal of Cutaneous Medicine and Surgery 2010;14:100–4.

[334] Coffin CS, Fraser HF, Panaccione R, et al. Liver diseases associated with anti-tumor necrosis factor-alpha (TNF-α) use for inflammatory bowel disease. Inflammatory Bowel Diseases 2011;17:479–84.

[335] Thomsen KL, Grønbæk H, Dahlerup JF, et al. Prednisolone but not infliximab aggravates the upregulated hepatic nitrogen elimination in patients with active inflammatory bowel disease. Inflammatory Bowel Diseases 2014;20:7–13.

[336] Bessissow T, Renard M, Hoffman I, et al. Review article: non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. Alimentary Pharmacology & Therapeutics 2012;36:312–23.

[337] Sebastian S, Ashton K, Houston Y, et al. Anti-TNF therapy induced immune neutropenia in Crohns disease—report of 2 cases and review of literature. Journal of Crohn's and Colitis 2012;6:713–6.

[338] Furst DE, Kay J, Wasko MC, et al. The effect of golimumab on haemoglobin levels in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Rheumatology 2013;52:1845–55.

[339] Katsanos K, Cavalier E, Ferrante M, et al. Intravenous iron therapy restores functional iron deficiency induced by infliximab. Journal of Crohn's and Colitis 2007;1:97–105.

[340] Matsumoto T, Nakamura I, Miura A, et al. New-onset multiple sclerosis associated with adalimumab treatment in rheumatoid arthritis: a case report and literature review. Clinical Rheumatology 2013;32:271–5.

[341] Ryu YS, Park SH, Kim JM, et al. A case of leukoencephalopathy associated with adalimumab-treated rheumatoid arthritis and a review of literature. Rheumatology International 2012;32:3481–5.

[342] Kaltsonoudis E, Voulgari PV, Konitsiotis S, et al. Demyelination and other neurological adverse events after anti-TNF therapy. Autoimmunity Reviews 2014;13:54–8.

[343] Nozaki K, Silver RM, Stickler DE, et al. Neurological deficits during treatment with tumor necrosis factor-alpha antagonists. American Journal of the Medical Sciences 2011;342:352–5.

[344] Caminero A, Comabella M, Montalban X. Tumor necrosis factor alpha (TNF-α), anti-TNF-α and demyelination revisited: an ongoing story. Journal of Neuroimmunology 2011;234:1–6.

[345] Gisbert JP, Marín AC, McNicholl AG, et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Alimentary Pharmacology & Therapeutics 2015;41:613–23.

[346] Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320–9.

[347] an Assche G, Lewis JD, Lichtenstein GR, et al. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: safety. American Journal of Gastroenterology 2011;106:1594–602.

[348] Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571–607.

[349] Dassopoulos T, Sultan S, Falck-Ytter YT, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 2013;145:1464–78.

[350] Carpio D, Jauregui-Amazaga A, de Francisco R, et al. Tuberculosis in anti-tumour necrosis factor-treated inflammatory bowel disease patients after the implementation of preventive measures: compliance with recommendations and safety of retreatment. Journal of Crohn's and Colitis 2016;10(10):1186–93.

[351] Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient. Annals of the Rheumatic Diseases 2011;70:1914–20.

[352] Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Annals of the Rheumatic Diseases 2010;69:380–6.

[353] Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Annals of the Rheumatic Diseases 2010;69:976–86.

[354] Galloway JB, Hyrich KL, Mercer LK, et al. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Annals of the Rheumatic Diseases 2011;70:1810–4.

[355] Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. American Journal of Gastroenterology 2012;107:1409–22.

[356] Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis

of randomized controlled trials. American Journal of Gastroenterology 2013;108:1268–76.

[357] Annese V, Duricova D, Gower-Rousseau C, et al. Impact of new treatments on hospitalisation, surgery, infection, and mortality in IBD: a focus paper by the Epidemiology Committee of ECCO. Journal of Crohn's and Colitis 2016;10:216–25.

[358] Magro F, Santos-Antunes J, Albuquerque A, et al. Epstein-Barr virus in inflammatory bowel disease-correlation with different therapeutic regimens. Inflammatory Bowel Diseases 2013;19:1710–6.

[359] Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clinical Gastroenterology and Hepatology 2011;9:30–5.

[360] Naganuma M, Kunisaki R, Yoshimura N, et al. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. Journal of Gastroenterology 2013;48:595–600.

[361] Serradori T, Germain A, Scherrer ML, et al. The effect of immune therapy on surgical site infection following Crohn's disease resection. British Journal of Surgery 2013;100:1089–93.

[362] Billioud V, Ford AC, Tedesco ED, et al. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta-analysis. Journal of Crohn's and Colitis 2013;7:853–67.

[363] Narula N, Charleton D, Marshall JK. Meta-analysis: peri-operative anti-TNFα treatment and post-operative complications in patients with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2013;37:1057–64.

[364] Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: a systematic review and meta-analysis. Journal of Crohn's and Colitis 2013;7:868–77.

[365] Ehteshami-Afshar S, Nikfar S, Rezaie A, et al. A systematic review and meta-analysis of the effects of infliximab on the rate of colectomy and post-operative complications in patients with inflammatory bowel disease. Archives of Medical Science 2011;7:1000–12.

[366] Huang W, Tang Y, Nong L, et al. Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: a meta-analysis of observational studies. Journal of Crohn's and Colitis 2015;9:293–301.

[367] Targownik LE, Bernstein CN. Infectious and malignant complications of TNF inhibitor therapy in IBD. American Journal of Gastroenterology 2013;108:1835–42.

[368] http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930T1.htm.

[369] Herrinton LJ, Liu L, Weng X, et al. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. American Journal of Gastroenterology 2011;106:2146–53.

[370] Siegel CA, Marden SM, Persing SM, et al. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clinical Gastroenterology and Hepatology 2009;7:874–81.

[371] Bernstein CN, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001;9:854–62.

[372] Loftus Jr EV, Tremaine WJ, Habermann TM, et al. Risk of lymphoma in inflammatory bowel disease. American Journal of Gastroenterology 2000;95:2308–12.

[373] Lewis JD, Bilker WB, Brensinger C, et al. Inflammatory bowel disease is not associated with an increased risk of lymphoma. Gastroenterology 2001;121:1080–7.

[374] Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54:1121–5.

[375] Afif W, Sandborn WJ, Faubion WA, et al. Risk factors for lymphoma in patients with inflammatory bowel disease: a case control study. Inflammatory Bowel Diseases 2013;19:1384–9.

[376] Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA 2014;311:2406–13.

[377] Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. New England Journal of Medicine 2015;372:1441–52.

[378] Annese V, Beaugerie L, Egan L, et al. European evidence-based consensus: inflammatory bowel disease and malignancies. Journal of Crohn's and Colitis 2015;9:945–65.

[379] Dulai PS, Thompson KD, Blunt HB, et al. Risk of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clinical Gastroenterology and Hepatology 2014;12:1443–51.

[380] Ferreri AJ, Govi S, Pileri SA. Hepatosplenic gamma-delta T-cell lymphoma. Critical Reviews in Oncology/Hematology 2012;83:283–92.

[381] Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clinical Gastroenterology and Hepatology 2011;9:36–41.

[382] Deepak P, Sifuentes H, Sherid M, et al. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha)inhibitors: results of the REFURBISH study. American Journal of Gastroenterology 2013;108:99–105.

[383] Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiology and Drug Safety 2011;20:119–30.

[384] Le Blay P, Mouferde G, Barnetche T, et al. Risk of malignancy including non-melanoma skin cancer with anti-tumour necrosis factor therapy in patients with rheumatoid arthritis: meta-analysis of registries and systematic review of log-term extension studies. Clinical and Experimental Rheumatology 2012;30:756–64.

[385] Mercer LK, Green AC, Galloway JB, et al. The influence of anti-TNF therapy upon incidence of keratinocytes skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. Annals of the Rheumatic Diseases 2012;71:869–74.

[386] Reachou P, Simard JF, Holmqvist M, et al. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. British Medical Journal 2013;346:f1939.

[387] Singh S, Nagpal SJ, Murad MH, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2014;12:210–8.

[388] Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and non-melanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143:390–9.

[389] Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews 2011;2:CD008794.

[390] Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. American Journal of Gastroenterology 2012;107:1409–22.

[391] Moran GW, Lim AW, Bailey JL, et al. Review article: dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2013;38:1002–24.

[392] Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–85.

[393] Moulis G, Sommet A, Bene J, et al. Cancer risk of anti-TNF-alpha at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. PLoS One 2012;7:e48991.

[394] Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Annals of the Rheumatic Diseases 2011;70:1895–904.

[395] Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA 2012;308:898–908.

[396] Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A pooled analysis of infections, malignancy, and mortality in infliximab-and immunomodulator-treated adult patients with inflammatory bowel disease. American Journal of Gastroenterology 2012;107:1051–63.

[397] Lichtenstein GR, Feagan BG, Cohen RD, et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT^{TM} Registry. American Journal of Gastroenterology 2014;109:212–23.

[398] Haynes K, Beukelman T, Curtis JR, et al. Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis & Rheumatology 2013;65:48–58.

[399] Biancone L, Orlando A, Kohn A, et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. Gut 2006;55: 228–33.

[400] Biancone L, Petruzziello C, Orlando A, et al. Cancer in Crohn's disease patients treated with infliximab: a long-term multicenter matched pair study. Inflammatory Bowel Diseases 2011;17:758–66.

[401] Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clinical Gastroenterology and Hepatology 2008;6:644–53.

[402] Williams CJM, Peyrin-Biroulet L, Ford AC. Systematic review with metaanalysis: malignancies with anti-tumour necrosis factor-α therapy in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2014;39: 447–58.

[403] Andersen NN, Pasternak B, Basit S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel diseases. JAMA 2014;311:2406–13.

[404] Biancone L, Armuzzi A, Scribano ML, et al. Inflammatory bowel disease phenotype as risk factor for cancer in a prospective multicentre nested case-control IG-IBD study. Journal of Crohn's and Colitis 2016;10(8):913–24.

[405] van der Woude JC, Kolacek S, Dotan I, et al. European evidenced-based consensus on reproduction in inflammatory bowel disease. Journal of Crohn's and Colitis 2010;4:493–510.

[406] Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. Rheumatology 2014;53:1377–85.

[407] Lichtenstein G, Cohen R, Feagan B, et al. Safety of infliximab in Crohn's disease: data from the 5000-patient TREAT registry. Gastroenterology 2004;126(Suppl. 4):A54.

[408] Katz JA, Antoni C, Keenan GF, et al. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. American Journal of Gastroenterology 2004;99:2385–92.

[409] Bortilik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. Inflammatory Bowel Diseases 2014;20:495–501.

[410] Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reproductive Toxicology 2014;43:78–84.

[411] Borltlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel disease exposed to anti-TNFα therapy during pregnancy: three-center study. Scandinavian Journal of Gastroenterology 2013;48:951–8.

[412] Gisbert JP, Chaparro M. Safety of anti-TNG agents during pregnancy and breastfeeding in women with inflammatory bowel disease. American Journal of Gastroenterology 2013;108:1426–38.

[413] Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clinical Gastroenterology and Hepatology 2013;11:286–92.

[414] Bröms G, Granath F, Ekbom A, et al. Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor agents during pregnancy. Clinical Gastroenterology and Hepatology 2016;14:234–41.

[415] Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab 2585 and infliximab in mothers and newborns, and effects on infection. Gastroenterology 2016;151(1):110–9.

[416] de Lima A, Zelinkova Z, van der Ent C, et al. Tailored anti-TNF therapy during 2588 pregnancy in patients with IBD: maternal and fetal safety. Gut 2015;65(8):1261–8.

[417] Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clinical Gastroenterology and Hepatology 2004;2:542–53.

[418] Osterman MT, Sandborn WJ, Colombel JF, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology 2014;146:941–9.

[419] Navarro JT, Ribera JM, Mate JL, et al. Hepatosplenic T-gammadelta lymphoma in a patient with Crohn's disease treated with azathioprine. Lymphoma 2003;44:531–3.

[420] Mackey AC, Greeen L, Liang LC, et al. Hepatosplenic T-cell lymphoma associated with Infliximab use in young patients treated with for inflammatory bowel disease. Journal of Pediatric Gastroenterology and Nutrition 2007;44:265–7.

[421] Shale MS, Kanfer E, Panaccione R, et al. Hepatosplenic T cell lymphoma in inflammatory bowel disease. Gut 2008;57:1639–41.

[422] Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. Journal of Crohn's and Colitis 2010;4:511–22.

[423] Sultan K, Korelitz BI, Present D, et al. Prognosis of lymphoma in patients following treatment with 6-mercaptopurine/azathioprine for inflammatory bowel disease. Inflammatory Bowel Diseases 2012;18:1855–8.

[424] McKenna MR, Stobaugh DJ, Deepak P. Melanoma and non-melanoma skin cancer in inflammatory bowel disease patients following tumor necrosis factor-α inhibitor monotherapy and in combination with thiopurines: analysis of the Food and Drug Administration Adverse Event Reporting System. Journal of Gastrointestinal and Liver Diseases 2014;23:267–71.

[425] Ulrich C, Degen A, Patel MJ, et al. Sunscreens in organ transplant patients. Nephrology Dialysis Transplantation 2008;23:1805–8.

[426] Papamichael K, Mantzaris GJ, Peyrin-Biroulet L. A safety assessment of anti-tumor necrosis factor alpha therapy for treatment of Crohn's disease. Expert Opinion on Drug Safety 2016;15:493–501.

[427] Shelton E, Laharie D, Scott FI, et al. Cancer recurrence following immune-suppressive therapies in patients with immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology 2016;151:97–109.

[428] Sandborn W, Feagan B, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. New England Journal of Medicine 2013;369:711–21.

[429] Sands B, Feagan B, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology 2014;147:618–27.

[430] Arniot A, Grimaud JC, Peyrin-Biroulet L, et al. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. Clinical Gastroenterology and Hepatology 2016;14(11):1593–601.

[431] Vivio EE, Kanuri N, Gilbertsen JJ, et al. Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. Journal of Crohn's and Colitis 2016;10:402–9.

[432] Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcer-2635 active colitis and Crohn's disease. Gut 2016, pii: gutjnl-2015-311079 [Epub ahead of print].

[433] Shahidi N, Bressler B, Panaccione R. The role of vedolizumab in patients with moderate-to-severe Crohn's disease and ulcerative colitis. Therapeutic Advances in Gastroenterology 2016;9:330–8.

[434] Colombel J, Sands B, Hanauer S, et al. Long-term safety of vedolizumab for the treatment of ulcerative colitis or Crohn's disease. American Journal of Gastroenterology 2013;108:S502.

[435] Wang M, Zhang L, Han W, et al. PRISMA—efficacy and safety of vedolizumab for inflammatory bowel diseases. Medicine 2014;93:e326.

[436] Katz S, Pardi D. Inflammatory bowel disease of the elderly: frequently asked questions (FAQs). American Journal of Gastroenterology 2011;106:1889–97.

[437] Sandborn W, Colombel J, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. New England Journal of Medicine 2005;353:1912–25.