Digestive and Liver Disease 49 (2017) 338–358

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

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 Chroric 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

Article history:
Received 9 October 2016
Received in revised form
19 December 2016
Accepted 7 January 2017
Available online 17 January 2017

Keywords:
Guidelines
Inflammatory bowel disease

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

List of attendees: Annalisa Aratari, Aurora Bortoli, Fabrizio Bossa, Maria Cappello, Andrea Cassinotti, Alberto Chiriatti, Gionata Fiorino, Vincenzo Formica, Luisa Guidi, Alessandra Losco, Filippo Mocciaro, Sara Onali, Luca Pastorelli, Roberta Pica, Mariabeatrice Principi, Sara Renna, Chiara Ricci, Antonio Rispo, Francesca Rogai, Loredana Sarmati, Franco Scaldaferri, Luisa Spina, Rosy Tambasco, Anna Testa, Angelo Viscido

* 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.

http://dx.doi.org/10.1016/j.dld.2017.01.141

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			
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; intraocular 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 infliximab 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 inflximab 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 ≥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.

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