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Progress Report

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☆

Ambrogio Orlando[a,*], Alessandro Armuzzi[b], Claudio Papi[c], Vito Annese[d], Sandro Ardizzone[e], Livia Biancone[f], Aurora Bortoli[g], Fabiana Castiglione[h], Renata D'Incà[i], Paolo Gionchetti[j], Anna Kohn[k], Gilberto Poggioli[l], Fernando Rizzello[j], Maurizio Vecchi[m], Mario Cottone[a]

[a] Department of Medicine, Pneumology and Nutrition Clinic, "V. Cervello" Hospital, Ospedali Riuniti "Villa Sofia-Cervello" University of Palermo, Palermo, Italy
[b] Internal Medicine and Gastroenterology Unit, Complesso Integrato Columbus, Catholic University, Rome, Italy
[c] Gastroenterology Unit, "San Filippo Neri" Hospital, Rome, Italy
[d] Gastroenterology Unit 2, Careggi University Hospital, Florence, Italy
[e] Department of Clinical Sciences, Chair of Gastroenterology, "Luigi Sacco" University Hospital, Milan, Italy
[f] Department of Internal Medicine, Chair of Gastroenterology, Tor Vergata University, Rome, Italy
[g] Gastroenterology Unit, Rho Hospital, Rho, Italy
[h] Department of Gastroenterology, Federico II University, Naples, Italy
[i] Department of Surgical and Gastroenterological Sciences, University of Padua, Italy
[j] Department of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy
[k] Department of Gastroenterology, "San Camillo-Forlanini" Hospital, Rome, Italy
[l] Department of General Surgery, University of Bologna, Bologna, Italy
[m] Gastroenterology and Gastrointestinal Endoscopy Unit, IRCCS San Donato Hospital, San Donato Milanese, Italy

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ABSTRACT

Biological therapies are an important step in the management of Inflammatory Bowel Diseases. In consideration of high cost and safety issues there is the need to have clear recommendations for their use. Despite the American Gastroenterological Association and the European Crohn's and Colitis Organisation have published exhaustive Inflammatory Bowel Disease guidelines, national guidelines may be necessary as cultural values, economical and legal issues may differ between countries. For these reasons the Italian Society of Gastroenterology and the Italian Group for the study of Inflammatory Bowel Disease have decided to elaborate the Italian guidelines on the use of biologics in Inflammatory Bowel Disease. The following items have been chosen: definitions of active, inactive, steroid dependent and resistant disease; measures of activity; anti-tumor necrosis factor alpha therapy use in active steroid dependent and refractory luminal Crohn's Disease, in fistulising Crohn's Disease, in steroid dependent and resistant active Ulcerative Colitis; risk of cancer; risk of infections during anti-tumor necrosis factor alpha therapy; special situations. These guidelines are based on evidence from relevant medical literature and clinical experience of a national working group.

1. Introduction

During the last 15 years biological therapy has been an important step forward in the treatment of Inflammatory Bowel Disease (IBD). Several Randomised Controlled Trials (RCTs) have allowed the role of these therapies to be defined. National guidelines have been published in order to provide homogeneous indications to their use [1–4]. In Europe the European Crohn's and Colitis Organisation (ECCO) have recently published the guidelines for the diagnosis and treatment of Crohn's disease (CD) and Ulcerative Colitis (UC) [5,6]. In these guidelines, as far as biological treatment is concerned, anti-tumor necrosis factor alpha (anti-TNFα) therapies are mainly considered because these are the only biologics which have been approved by the European Medicine Agency (EMEA) and more than 40% of the statements are based on the recommendations of experts. Up to today, no guidelines regarding the use of biologics in adult patients with IBD have been published in Italy. The only biologics approved are infliximab in CD and UC and adalimumab in CD. National guidelines may be necessary as cultural values, economical and legal issues may differ between countries

☆ See Appendix A for the list of experts.

* Corresponding author. Tel.: +39 3385942487; fax: +39 0916885111.
E-mail address: ambrogiorlando@tiscali.it (A. Orlando).

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[7]. For this reason the Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) have decided to elaborate the Italian guidelines on the use of biologics in IBD.

Fifteen experts of Italian IBD referral centers belonging to the IG-IBD had been invited to join a meeting where the main issues of TNFα antagonist therapy have been identified. The following items have been chosen: definitions of active, inactive, steroid dependent and resistant disease; measures of activity; anti-TNFα therapy use in active steroid dependent and refractory luminal CD, in fistulising CD, in steroid dependent and resistant active UC; risk of cancer; risk of infections during anti-TNFα therapy; special situations. Each expert was invited to formulate provisional statements on one of these topics and to justify the statements according to current scientific evidence. The Oxford methodology was used to establish levels of evidence and degree of recommendations (Table 1) [8]. A complete research thorough Pub Med, Embase, Cochrane database was done by each expert in order to formulate recommendations. After statement elaboration, a further 14 Italian experts belonging to the IG-IBD (from the referral gastroenterological centers and non-referral gastroenterological centers) together with a national representative of the association of patients with IBD (Associazione Malattie Infiammatorie Croniche Intestinali: AMICI) were invited to participate to 3 consensus conferences (one in Bologna and 2 in Rome) in which the provisional statements were discussed with the 15 experts and an agreement on the statements was reached. If there was a disagreement amongst the 30 partecipants an agreement on the statements was reached by vote (51% of partecipants).

Table 1
Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence Based Medicine [8].

Level	Individual study	Technique
1a	Systematic review (SR) with homogeneity of Level 1 diagnostic studies	Systematic review (SR) with homogeneity of randomised controlled trials (RCTs)
1b	Validating cohort study with good reference standards	Individual RCT (with narrow Confidence interval)
1c	Specificity is so high that a positive result rules in the diagnosis ("SpPin") or sensitivity is so high that a negative result rules out the diagnosis ("SnNout")	All or none
2a	SR with homogeneity of level > 2 diagnostic studies	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c		"Outcomes" research; ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case–control studies
3b	Non-consecutive study; or without consistently applied reference standards	Individual case–control study
4	Case–control study, poor or non-independent reference standard	Case-series (and poor quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of recommendation

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolation from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

1.1. Definitions

With respect to the definitions of IBD, the participants have tried to reach an overall agreement about commonly used terms. Although some of the used definitions are arbitrary, they reflect the every day practice of clinical decision-making.

1.1.1. Definitions of CD

IG-IBD Statement 1
RESPONSE: ΔCDAI $\geq$ 100 points or Δ HBI $\geq$ 3
REMISSION: CDAI < 150 or a HBI < 4, without steroids
RELAPSE: A flare of symptoms with a CDAI > 150 or a HBI > 4 in a patient in clinical remission
RECURRENCE: The appearance of new CD lesions after curative resection of macroscopic disease, usually in the neoterminal ileum and/or at the anastomotic level, detected by endoscopy, radiology, or surgery
STEROID-REFRACTORY CD: Active disease in spite of an adequate dose and duration of prednisone (0.75–1 mg/kg/day for at least 2 weeks)
STEROID-DEPENDENT CD: inability to stop systemic steroids within 3 months or budesonide within 6–9 months, without clinical relapse or relapse within 3 months after steroid weaning

1.1.1.1. Active disease. Clinical disease activity is classified into mild, moderate, and severe according to the CD activity (CDAI) or the Harvey–Bradshaw (HBI) indexes [9,10]. Mild disease is defined with a CDAI value between 150 and 220 or with a HBI value between 5 and 7. Moderate disease is defined with a CDAI value between 220 and 450 or with a HBI value between 8 and 16. Severe disease is defined with a CDAI value > 450 or with a HBI value > 16 [11]. In clinical practice, however, the evaluation of disease activity is subjected to the overall clinical condition, together with laboratory, endoscopy and imaging findings.

1.1.1.2. Response. Response is defined by a decrease of CDAI of at least 100 points (ΔCDAI $\geq$ 100) [6]. In the past years, some studies, including those initially evaluating the effectiveness of infliximab, considered a softer endpoint of response with a reduction in CDAI > 70 points or more from the baseline value and at least a 25% reduction in the total score [12–14]. It has been recently reported that a decrease in the HBI index $\geq$ 3 points closely correlates with a ΔCDAI $\geq$ 100, thus allowing a simpler Crohn's disease activity assessment [15].

1.1.1.3. Remission. Most of the clinical trials, including studies on the efficacy of biologics in CD, have adopted the definition of disease in clinical remission when the CDAI is <150 [11]. It has recently been reported that a HBI index < 4 points closely correlates with a CDAI < 150 points, thus allowing a simpler Crohn's disease activity assessment [15].

1.1.1.4. Relapse. A flare-up of symptoms with a CDAI > 150 or a HBI > 4 in a patient with an established CD who is in clinical remission. Other definitions have been proposed for the purposes of clinical trials, but there is a disagreement about this issue [16]. In clinical practice, however, the evaluation of a disease

relapse is subjected to the overall clinical condition, laboratory, endoscopy and imaging. Early relapse is defined as a clinical relapse within 3 months after achieving remission with a previous therapy.

1.1.1.5. Recurrence. The term recurrence is best used to define the reappearance of disease after curative surgical resection. Recurrence is commonly classified as clinical and morphological. Clinical recurrence is defined as the appearance of symptoms after surgical resection, provided that recurrence of lesions is confirmed [17]. Morphological recurrence is defined as the appearance of new lesions after curative surgical resection, even in the absence of overt symptoms, usually located at the neo-terminal ileum and/or anastomosis. The severity of morphological recurrence is commonly graded endoscopically using the Rutgeerts score [18]. Other diagnostic techniques (ultrasound, computed tomography, magnetic resonance imaging) proposed to assess morphological recurrence have not yet been widely accepted.

1.1.1.6. Steroid-refractory CD. Steroid-refractory CD is defined as an active disease in spite of an adequate dose and duration of prednisone therapy (0.75–1 mg/kg/day or equivalent for at least 2 weeks).

This definition is slightly different from the ECCO guidelines [16]. There was a complete agreement amongst participants about the duration of steroid therapy, since the timing of biologic therapy is continually changing.

1.1.1.7. Steroid-dependent CD. Steroid-dependent CD is defined as (1) the inability to stop systemic steroids within 3 months or budesonide within 6–9 months of starting therapy, without clinical relapse, or as (2) a relapse within 3 months after steroid weaning. Many definitions have been proposed, mainly based on clinical experience and not on physiopathologic evidence [16,19]. Despite these limitations, an arbitrary definition of steroid dependency is useful as guidance for clinical practice.

2. Definitions of Ulcerative Colitis

IG-IBD Statement 2
RESPONSE: Clinical and endoscopic improvement according to the activity index used
REMISSION: Stool frequency $\leq$ 3/day with no bleeding or urgency
RELAPSE: Flare of symptoms in a patient who is in clinical remission
ORAL STEROID-REFRACTORY UC: Active disease in spite of an adequate dose and duration of prednisone therapy (0.75–1 mg/kg/day or equivalent for at least 2 weeks)
I.V. STEROID-REFRACTORY UC: Persistent active disease or worsening despite equivalent methylprednisolone 1 mg/kg/day i.v. over a period of 1 week
STEROID-DEPENDENT UC: inability to stop steroids within 3 months of starting therapy, without clinical relapse, or relapse within 3 months after steroid weaning

2.1. Active disease

Clinical disease activity is classified into mild, moderate, and severe according to the Truelove and Witts' criteria [20]. In clinical practice, sigmoidoscopy is advisable to confirm disease activity, severity and extent. Many other activity indexes have been proposed. Amongst them, the Mayo score, which includes endoscopic grading of disease, could be a valid alternative to evaluate disease activity [21].

2.2. Response

Response is commonly defined as clinical and endoscopic improvement, according to the activity index used. In clinical practice, however, response is better defined as symptom improvement vs baseline. In clinical trials when the Mayo score is used, response is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 percent, with a decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1 [21–23].

2.3. Remission

In clinical practice, remission is defined as a stool frequency $\leq$ 3/day, with no bleeding and no urgency; sigmoidoscopy to confirm mucosal healing is generally unnecessary [24]. However, the combination of clinical and endoscopic activity is appropriate for clinical trials. When the Mayo score is used, remission is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point [21,25].

2.4. Relapse

A flare-up of symptoms in a patient with an established UC who is in clinical remission. Rectal bleeding alone or in combination with an increase in stool frequency are considered the essential clinical components of relapse. Endoscopic evaluation is not always necessary. However, the combination of clinical and endoscopic activity is appropriate for clinical trials [21].

Early relapse is defined as a clinical relapse within 3 months after achieving remission with a previous therapy. There is no agreement about the definitions of pattern of relapse. In clinical practice, patterns of relapse are conventionally classified as infrequent when relapse occurs no more than once a year, frequent when relapse occurs at least twice a year, or continuous when symptoms are persistent without a period of remission, irrespective of concomitant therapy [26].

2.5. Steroid-refractory UC

2.5.1. Oral steroid-refractory UC

Active disease in spite of an adequate dose and duration of prednisone therapy (0.75–1 mg/kg/day or equivalent for at least 2 weeks). This definition is slightly different from the ECCO guidelines [22]. There was a complete agreement amongst the participants about the duration of steroid therapy, since the timing of biologic therapy is continually changing.

2.5.2. Intravenous steroid-refractory UC

Persistent active disease or worsening despite equivalent methylprednisolone 1 mg/kg/day i.v. over a period of 1 week. There was a complete agreement amongst the participants about the duration of intravenous steroid therapy, even if in this particular setting of patients a rescue therapy or surgery is subjected to the overall clinical and laboratory condition.

2.6. Steroid-dependent UC

Steroid-dependent disease is defined as (1) the inability to stop steroids within 3 months of starting therapy, without clinical relapse or as (2) relapse within 3 months after steroid weaning. Several definitions have been proposed, mainly based on clinical experience and not on physiopathologic evidence [1,21,22]. Despite

these limitations, an arbitrary definition of steroid dependency is useful as guidance for clinical practice.

3. Activity indexes to be monitored

IG-IBD Statement 3A
Clinical activity should be monitored during induction and maintenance therapy with Anti-TNFα to support the efficacy of treatment: the Harvey–Bradshaw Index (HBI) could be the best choice in clinical practice for CD [EL 1b, RG B], the Modified Truelove & Witts Severity Index (MTWSI) for UC [EL 3b, RG C]

The best clinical outcome in the treatment of IBD patients is steroid-free remission. In the real clinical setting, however, clinical response could be an acceptable endpoint of therapeutic success.

Different tools have been designed to measure either the clinical or the endoscopic activity of the disease and surrogate markers are available to substantiate the clinician's judgement.

The use of clinical and endoscopical indexes is questionable in everyday clinical practice whilst they are undoubtely required in research settings: the clinician and the patient need more user-friendly tools to assess the response to treatments.

The CDAI is widely considered the gold standard even if it does not take into account the endoscopic activity [9]. The tool is not routinely used in clinical practice especially because it requires a 7-day data collection by the patient in a diary. The Harvey–Bradshaw Index (HBI) is used as alternative to assess clinical activity since it is simpler to use and does not require a patient's data collection, and it correlates with the CDAI [10,15].

In UC Truelove and Witts' criteria [20] and the Modified Truelove & Witts Severity Index (MTWSI) [27] are widely used in clinical trials for assessing the degree of disease severity. According to the relevance recently attributed to mucosal healing, the Mayo score [28] should probably be preferred even if it requires a patient data collection on the last 3 days before the clinical examination.

IG-IBD Statement 3B
The Perianal Disease Activity Index is a validated index for measuring treatment outcomes in perianal CD, [EL 1b, RG B] but it should be integrated with examination under anaesthesia [EL 2b, RG C], trans-anal ultrasonography [EL 1b, RG B] and/or magnetic resonance imaging [EL 1b, RG B] performed by experienced specialists where these services are available

The Perianal Disease Activity Index (PDAI) has been used in clinical trials [29]. It can be considered the perianal equivalent of the CDAI, but additional research is needed to determine the minimum clinically significant difference and the "cut off" value indicating remission. In clinical practice perianal disease is commonly evaluated through the combination of clinical symptoms, trans-anal ultrasonography or magnetic resonance imaging or examination under anesthesia.

IG-IBD Statement 3C
Efficacy of treatment in modifying patients' Quality of Life should be measured [EL 1b, RG B]
Patient reported general well being can be assessed simply by using a Visual Analogical Scale [EL 1a, RG A]

The Inflammatory Bowel Disease Questionnaire (IBDQ) [30] has been used extensively as a secondary endpoint in clinical trials [31]. It is recommended to use this tool in order to ensure that quality of life is improved in medically treated patients.

Single-item measures, like the Visual Analogical Scale (VAS) are parsimonious alternatives to multiple-item measures in many types of assessment [32].

This type of assessment has yet to be used in the clinical research setting, but its role in the real clinical setting needs to be studied.

IG-IBD Statement 3D
CRP can be used to monitor patients, especially in CD, mainly because of its cheapness, wide availability and immediacy. If available, hs-CRP or wr-CRP should be preferred [EL 1b, RG B]

The production of C-reactive protein (CRP) occurs as part of the acute phase response upon stimulation by several cytokines originating at the site of inflammation. Its short half-life makes CRP a valuable marker to follow up disease activity. Patients with CD have stronger CRP response than UC patients but levels correlate well with disease activity and extent [33]. The introduction of high sensitivity CRP (hs-CRP) has offered further advantages demonstrating that the slope of correlation between levels and activity are the same in UC and in CD even if in absolute, hs-CRP levels might be lower especially in patients with a distal disease [34]. The use of wide-range CRP (wr-CRP) might represent the future evolution because it can be determined in real-time at a low-cost and offers significant correlation with hs-CRP [35].

Faecal lactoferrin and calprotectin are highly sensitive and specific markers for detecting intestinal inflammation [36–38]. Intestinal permeability is a surrogate marker of intestinal inflammation (38) and is a good predictor of relapse in CD [39,40].

4. Induction and maintenance of remission in moderate-to-severe steroid-refractory or dependent Crohn's disease

IG-IBD Statement 4A
Anti-TNFα agents are a valuable option (infliximab [EL 1b, RG A], adalimumab [EL 1b, RG B]) in moderate-to-severe steroid-refractory or dependent CD
Thiopurines could be added in naïve patients [EL 1b, RG B]
Adalimumab can be used as a second line treatment in patients with primary failures to infliximab [EL 4, RG C] or with loss of response or intolerance to infliximab [EL 1b, RG B]

Anti-TNFα therapy has been evaluated as an induction and maintenance therapy in CD in several RCTs and meta-analyses [41–43], showing efficacy in both clinical settings. However, in most trials the inclusion criteria have been heterogeneous including both patients with an active disease naïve to steroid and with steroid-refractory or dependent disease.

Only one trial has been designed to assess the role of infliximab as an induction treatment in steroid-dependent CD [44]. In this trial, infliximab plus Azathioprine/6-Mercaptopurine (AZA/6-MP) was compared to AZA/6-MP alone in corticosteroid-dependent Crohn's disease patients. The primary endpoint was remission off steroids at week 24. Amongst the 113 enrolled patients, 57 were assigned to infliximab. At week 24, the success rate (intent-to-treat analysis) was higher in the infliximab group than in the placebo group (57% vs 29%; $p = 0.003$); at weeks 12 and 52, the corresponding rates were 75% vs 38% ($p < 0.001$) and 40% vs 22% ($p = 0.04$), respectively. In the

subgroup of patients naïve to AZA/6-MP the corresponding figures were 63% and 32% ($p = 0.02$); conversely in patients with previous AZA/6-MP failures the differences were not statistically significant.

No trial has been designed on the maintenance of corticosteroid-dependent patients. The data of efficacy on this population can be extrapolated from the results of ACCENT I trial in which 51% of patients received corticosteroids at the time of randomisation. 24% of those maintained on infliximab every 8 weeks at 5 mg/kg and 32% of those receiving 10 mg/kg were in corticosteroid-free clinical remission at week 54. Only 9% of patients receiving placebo maintained corticosteroid-free remission ($p = 0.004$ for infliximab groups vs placebo) [13]. Similar data was obtained in the Charm study with scheduled adalimumab [42]. In particular, 44% of patients were receiving steroids at enrolment and 6%, 29%, and 23% of patients treated with placebo, adalimumab 40 mg every other week, and adalimumab 40 mg weekly, respectively, achieved corticosteroid-free clinical remission ($p < 0.001$ for adalimumab 40 mg every other week vs placebo; $p < 0.008$ for adalimumab 40 mg weekly vs placebo) at week 56.

In the recent Sonic study in patients naïve to anti-TNFα therapy and thiopurines combination therapy seemed to be more effective even if the trial did not specifically address steroid-dependent CD patients [45]. In the case of primary failure to infliximab, adalimumab has been shown to induce remission in the short term in 28% of patients [46]. In the Gain study it was shown that 22% of patients with loss of response or previous intolerance to infliximab (secondary infliximab failures) achieved remission with adalimumab compared with 5% of the placebo group [47].

4.1. Maintenance of remission in luminal CD

IG-IBD Statement 4B
Anti-TNFα agents (infliximab and adalimumab) are effective for maintenance of remission up to 1 year in patients with clinical response to induction therapy [EL 1a, RG A]
Anti-TNFα agents should be the treatment of choice for patients who have failed maintenance strategies with immunosuppressants [EL 1b, RG B]

IG-IBD Statement 4C
Open experiences have reported long-term effectiveness and safety of anti-TNFα agents; however, the duration of the therapy over 1 year should be carefully evaluated on a case-by-case basis [EL 4, RG C]

There are only a few randomised clinical trials specifically aimed at evaluating the long-term maintenance treatment of Crohn's disease by means of biologics [12,13,42,48]. These studies have usually followed-up patients for a maximal time period of only 1 year, which could be considered a short time, compared with a life-long disease.

A systematic Cochrane review was based on 3 studies on infliximab and 2 on adalimumab [49]. As far as infliximab is concerned, the meta-analysis concluded that scheduled infliximab (5–10 mg/kg every 8 weeks) is better than placebo for maintaining remission over 1 year (RR: 2.5–95% CI 1.64–3.80). Similar data is obtained combining 2 studies addressing adalimumab for maintaining remission over 1 year. The overall effects favour adalimumab (40 mg every other week or weekly) compared to placebo (RR: 2.86–95% CI 2.1–4.2). No significant differences between 5 and 10 mg/kg of infliximab every 8 weeks or between adalimumab 40 mg every other week or every week has been observed in the maintenance phases.

Thus, the less expensive combination should be the treatment of choice at the beginning. However, dose increase and/or time reduction might be effective strategies for those patients showing reduction of efficacy during follow-up.

Recently, the Sonic study compared three different treatments (infliximab alone, azathioprine alone and a combination therapy) for inducing and maintaining remission in moderate-severe CD [45]. At 26 weeks the steroid-free remission rates in patients receiving combined immunosuppressive therapy with infliximab and AZA were higher than with the infliximab monotherapy (57% vs 45%, $p < 0.05$) and these were also higher than remission rates in patients with AZA monotherapy (45% vs 30%, $p < 0.01$). Whether combined AZA/6-MP and anti-TNFα therapy increases long-term toxicity is still debated, but the recent emergence of 28 hepatosplenic T cell lymphomas in young Crohn's disease patients with combined therapy have raised considerable concern [50–52].

As far as long-term maintenance therapy is concerned, there is evidence that adalimumab is able to maintain remission for up to 2 years in patients who responded to induction therapy [53] and that long-term infliximab treatment has a good overall safety profile in cohort studies [54].

Although these open prospective studies seem to have a safe maintenance efficacy for long-term periods, the duration of the therapy over 1 year should be carefully evaluated on a case-by-case basis and discussed with the patient.

4.2. Early treatment in CD

IG-IBD Statement 4D
Early use of Biologics may improve patient outcomes in active CD [EL 2b, RG B]
However, a widespread use of a "top down" approach in all CD patients cannot be recommended
Clinical factors at diagnosis may predict poor outcome in CD and should be taken into account when determining the initial therapeutic approach [EL 2b, RG C]. However, the benefit of early treatment with biologics in this patient subgroup is not proven

Increasing experience with anti-TNFα strategies in severe refractory CD has raised the question whether an early use can improve patients outcomes. In a randomised controlled trial on 133 patients with moderate-to-severe CD of recent onset (less than 4 years) and corticosteroids/immunosuppressants naïves, it has been shown that early combined infliximab and immunosuppressants treatment is better than the conventional step up approach in terms of remission off steroids or surgery at 6 and 12 months. The absolute benefit increase in the early infliximab group is 24.1% (95% CI 7.3–40.8) at 6 months, and 19.3% (95% CI 2.4–36.3) at 12 months [55]. However, we do believe that in this trial the conventional step up approach was suboptimal as far as the systemic steroid dose (40 mg/day), the use of budesonide, and the late introduction of immunosuppressants is concerned. These observations weaken the strength of the conclusion of the statement.

Subgroup analysis of the CHARM study (adalimumab) suggests that patients with disease duration of less than 2 years had approximately 20% increase in remission rates at 26 and 56 weeks compared to patients with disease duration of longer than 5 years [56].

Taken together, these data suggest that there may be a window of opportunity in which biologic therapies may have the most impact but do not provide enough strong evidence that an early treatment can improve patient outcomes in terms of response and remission. Therefore, a widespread early use of biologics in all CD patients cannot be recommended. However, in specific patient subgroups with a predictable disabling severe course (extensive disease, severe rectal disease, young age, severe perianal diseases at diagnosis, steroid need at diagnosis) the early introduction of biologics can be empirically considered on an individual basis [57].

Mucosal healing has not yet been considered as a primary or secondary endpoint in most of the randomised controlled trial addressing biologic therapies. Available data comes from endoscopic evaluation of subgroup of patients or observational studies. Mucosal healing with infliximab treatment can be expected in 30% up to 70% of patients [45,55,58,59]. There is some evidence that mucosal healing predicts a sustained remission and a better outcome [59–61] but there is insufficient evidence to recommend regular colonoscopic evaluation in patients receiving anti-TNFα therapy. Only one study has evaluated the efficacy of scheduled adalimumab over 1 year considering mucosal healing as a primary endpoint. At week 52, 24% of patients receiving scheduled adalimumab achieved mucosal healing compared to 0% of patients receiving adalimumab induction only ($p = 0.001$) [62].

5. Management of perianal fistulae

The advent of biologics has dramatically changed the therapeutic approach to perianal fistulising disease. Moreover the introduction of new image technics such as Magnetic Resonance Imaging (RNI) and Endoscopic Ultrasound (EUS) has provided new insights into the anatomical definition of perianal fistulas. For this reason in this section we have considered the global approach to perianal disease including diagnostic work-up, pharmacological strategies and surgical approach.

The main aspects to be taken into account when planning a strategy for the management of CD fistulas are:

- Locate the origin of the fistula and its anatomy.
- Evaluate the originating intestinal loop (inflammation or stenosis).
- Identify or exclude local sepsis (abscess).
- Determine which organs are affected and their contribution to systemic symptoms or impairment of the quality of life.

5.1. Diagnosis and anatomical classification

IG-IBD Statement 5A
Pelvic MRI should be the initial procedure complementing EUA because it is accurate and non-invasive, although it is not needed routinely in simple fistulae [EL 2b, RG B]
EUA is considered the gold standard only in the hands of an experienced surgeon [EL 5, RG D]
EUS requires expertise, but can be equivalent to MRI in complementing EUA if rectal stenosis has been excluded [EL 2b, RG B]
Fistulography is not recommended [EL 3, RG C]
As the presence of concomitant rectosigmoid inflammation has prognostic and therapeutic relevance, proctosigmoidoscopy should be used routinely in the initial evaluation [EL 2b, RG B]

Various tools have been described, including Exam Under Anesthesia (EUA), fistulography, and imaging by EUS or RMI.

EUA is reported to be the most sensitive tool, with an accuracy of 90% [63,64]: it has the advantage of permitting concomitant surgery. MRI has an accuracy of 76–100% for fistulas and may provide additional information [64,65]. EUS has an accuracy of 56–100%, especially when performed by experts in conjunction with hydrogen peroxide enhancement [66–68]. Any of these methods should be combined with the endoscopy to assess the presence or absence of inflammation in the rectosigmoid colon.

Various classifications have been proposed, either relating fistulas to the ano-rectal ring (high or low), or in more precise anatomical terms where the external sphincter is the reference point, described by Parks [69]. A more empiric and easier classification into simple (minimal involvement of the sphincter without rectal inflammation) and complex (large involvement of the sphincter or simple fistula with recatl inflammation) fistulas has been proposed [70]. This assessment includes the physical inspection of the area to detect fistulous connections, strictures, and abscesses, together with the endoscopic evaluation of the rectosigmoid area for the presence or absence of macroscopic inflammation.

5.2. Treatment

IG-IBD Statement 5B
The presence of a perianal abscess should be ruled out and if present should be drained as a matter of urgency [EL 5, RG D]

IG-IBD Statement 5C
Simple perianal fistulas should be treated either with fistulotomy (in extra or intersphincteric tract) or with placement of loose seton [EL 3, RG D]. Antibiotics, metronidazole (750–1500 mg/day), and/or ciprofloxacin (1000 mg/day), could be added in the presence of sepsis [EL 3, RG D]. Biological therapy is not indicated

5.2.1. Medical therapy

Even if, for many years, metronidazole and ciprofloxacin have been recommended as first line therapy, there is no controlled evidence of their efficacy [71–75]. There are also no RCTs assessing the effect of AZA or 6-MP on the closure of perianal fistulas as primary endpoint in CD. Data favouring the use of these drugs comes from a meta-analysis of five RCTs where perianal fistula closure was assessed as a secondary endpoint [76,77], in addition to uncontrolled case series. Small uncontrolled series suggest that intravenous cyclosporine A, may be effective for inducing short term fistula improvement or closure [78]. A small, placebo-controlled trial showed that oral tacrolimus 0.2 mg/kg/day was better than placebo in improving (closure of at least 50% of fistulas), but not in inducing remission (closure of 100% of fistulas), in perianal CD after 4 weeks [79].

Finally case reports and uncontrolled case series have reported benefit, from enteral or parenteral nutrition, mycophenolate mofetil, methotrexate, thalidomide, granulocyte colony stimulating factor, and hyperbaric oxygen, but they are not recommended as a standard practice [80].

5.2.2. Anti-TNF agents

IG-IBD Statement 5D
Complex fistulas:
"Cone-like" fistulectomy of each fistula tract should firstly be performed with sparing of sphincteric structures [EL 4, RG D]. Seton placement should be recommended [EL 4, RG D], the timing of removal depending on subsequent therapy. Anti-TNFα agents should be used as the first choice of medical therapy for complex perianal CD [infliximab EL1b, RG A; adalimumab EL1b, RG B]. Combination with surgical therapy is recommended despite a lack of clinical trials [EL 4, RG D]. Antibiotics and/or azathioprine/6-mercaptopurine should be used as a second line medical treatment, despite a lack of clinical trials [EL 4 RG D]

IG-IBD Statement 5E
In evaluating the response to medical and/or surgical treatment in routine practice, combined medical and surgical clinical assessment in combination with MRI is now considered mandatory [EL 2b, RG D]

IG-IBD Statement 5F
Maintenance therapy after successful anti-TNFα agents induction is mandatory. Infliximab [EL 1b, RG A], adalimumab [EL 1b, RG B], or AZA/6-MP [EL 2b, RG C], with drained sepsis [EL 4, RG B], should be used as maintenance therapy. All the maintenance therapy should be used for at least 1 year [EL 1b, RG A]; adalimumab could be used up to 3 years [EL 2, RG B]

IG-IBD Statement 5G
In the event of infliximab secondary failure the use of adalimumab is recommended [EL 2, RG B]. In case of anti-TNFα agents failure, azathioprine/6-mercaptopurine or methotrexate [EL 5, RG D] or tacrolimus [EL 1b, RG B], with antibiotics as adjunctive treatment, is another therapeutic choice. Depending on the severity of the disease, a diverting ostomy can be performed later, or proctectomy as the last resort [EL 5, RG D]

5.2.2.1. Infliximab. Infliximab was the first agent shown to be effective in an RCT for inducing closure of perianal fistulas and for maintaining this response for 1 year. In the first RCT an induction regimen of 5 mg/kg infusions at weeks 0, 2, and 6 induced complete closure (cessation of all drainage on two visits 1 month apart) in 55% of cases compared to 13% in the placebo group ($p = 0.001$) [81]. In the ACCENT II trial at week 54, 36% on infliximab had complete closure compared with 19% receiving placebo ($p = 0.009$) [82]. Maintenance infliximab reduces hospitalisation and surgery.

5.2.2.2. Adalimumab. No controlled trials addressed the efficacy of adalimumab in perianal fistulising CD. In the Classic 1 study, in a very small patient subgroup with draining fistulas (32/299), no difference in inducing fistula closure in the short term, was observed between adalimumab and placebo [14]. In the Gain study a subgroup of 45/325 had perianal fistulas: no difference was found between adalimumab and placebo for fistula response and closure [47].

As far as the maintenance treatment is concerned, a subgroup analysis of the Charm study shows that complete fistula closure has been observed in 33% of adalimumab treated patients vs 13% of patients in the placebo group ($p = 0.016$) [42]. All patients received 80 mg/40 mg adalimumab induction and at week 4 they were randomised to receive either 40 mg weekly, 40 mg every other week or placebo injections for 1 year. Of all patients with healed fistulas at week 56 (both adalimumab and placebo groups), 90% (28/31) maintained healing following 1 year of open-label adalimumab therapy [82].

There is no data on the effect of AZA/6-MP as maintenance therapy for fistulas after induction with infliximab or adalimumab, or during infliximab maintenance therapy. Around 75% of patients in the ACCENT II trial were already taking AZA/6-MP before recruitment, but this medication was continued together with infliximab in only 30% of cases [83]. This implies that although infliximab maintained longer fistula closure than placebo in this trial, it occurred with AZA/6-MP as background therapy in some cases.

5.3. Surgical procedures for perianal CD

IG-IBD Statement 5H
Surgical treatment is mandatory both for simple and complex fistulas. It includes abscess drainage, fistulotomy, fistulectomy, and loose seton placement.
A diverting ostomy or proctectomy may be necessary for severe disease refractory to medical therapy. Complete fistulectomy should not be performed because of the risk of incontinence. A more complex surgical procedure such as an endoanal advancement flap should be an attractive option in absence of rectal disease and a single source is easily identified [EL 4a, RG D]

Surgical treatment is sometimes necessary for simple fistulas, but it is always necessary for complex perianal disease. It includes abscess drainage, fistulotomy, and Seton placement, according to the symptoms caused by the location and complexity of the fistulas. A diverting ostomy or proctectomy may be necessary for severe disease refractory to medical therapy. Traditional fistulectomy and fistulotomy should not be performed, because of the risk of incontinence and later the need of a proctectomy.

5.3.1. Surgical intervention in conjunction with anti-TNFα treatment

There is concern about anti-TNFα treatment in the presence of undetected perianal sepsis. Surgery (by EUA) for perianal disease includes abscess drainage, fistulotomy, and Seton placement, and may be important to optimise therapeutic results as well as avoiding septic complications.

During the last 5 years, several small controlled trials have shown that the combination of Seton and infliximab is superior to Seton or infliximab, probably because of better drainage of abscesses and fistulae [84]. The combination gives better response [85], longer effect duration [86] and lower recurrence rate. Moreover, reparative surgery during the period of infliximab treatment may improve long-term healing rates [87].

6. Induction and maintenance of response/remission in moderate-to-severe steroid-refractory or steroid-dependent Ulcerative Colitis

IG-IBD Statement 6A
Infliximab induction regimen can be used in patients with moderate-to-severe UC who are refractory to systemic corticosteroids [EL 1b, RG A] and in corticosteroid-dependent patients who are intolerant/refractory to thiopurines [EL 2b, RG C]

IG-IBD Statement 6B
One year scheduled treatment with Infliximab can be used in patients who have responded to infliximab induction [EL 1b, RG A]. In patients who are thiopurine-naïve, maintenance therapy with thiopurines alone is a valuable option [EL 5, RG D]. The duration of the therapy over 1 year should be carefully evaluated on a case-by-case basis [EL 4, RG C]. Maintenance therapy with infliximab that achieves only response should be carefully evaluated in the face of a colectomy [EL 5, RG D]

The goals of biologic therapy in UC include induction and long-term maintenance of corticosteroid-free remission [88]. One-year outcome of a population-based study showed that 22% and 29% of patients with UC treated with systemic corticosteroids became steroid-dependent or steroid-refractory, respectively, with the need of colectomy [89]. In patients with active steroid-refractory or steroid-dependent UC thiopurines may be an effective therapy [90–92].

As far as the efficacy of infliximab in moderate-to-severe UC refractory to corticosteroids and/or immunomodulators is concerned, two systematic reviews concluded that infliximab was more effective than placebo in inducing clinical response (RR 1.99, 95% CI 1.65–2.41), clinical remission (RR 3.22, 95% CI 2.18–4.76), mucosal healing (RR 1.88, 95% CI 1.54–2.28) at 8 weeks. The number needed to treat (NNT) with infliximab to achieve short- and long-term response or remission were 3–4 and 3–5, respectively [93,94].

Two randomised placebo-controlled trials have evaluated the efficacy of infliximab for induction and maintenance of remission in patients with moderate-to-severe active UC, despite treatment with concurrent medications (Active UC Trials 1 and 2: ACT 1 and ACT 2) [23]. The patients with steroid-refractory disease were about 30% in both trials, whilst the real number of patients with steroid-dependent disease was not clear because the definition of steroid dependency was not described. Moreover, in the ACT 2 study 26% of patients were refractory to 5-ASA alone. The primary endpoint was clinical response at week 8. This was achieved in both the studies, with significant differences between active arms (infliximab 5 or 10 mg/kg) and placebo. Clinical remission at week 8 was achieved in 14.9% (placebo), 38.8% (5 mg/kg) and 32.0% (10 mg/kg) in the ACT 1 trial ($p < 0.001$ and $p = 0.002$ vs placebo, respectively) and in 5.7% (placebo), 33.9% (5 mg/kg) and 27.5% (10 mg/kg) in the ACT 2 trial ($p < 0.001$ for both comparisons with placebo). Clinical response and remission were significantly maintained compared with placebo through week 30 and 54. Infliximab was also significantly more effective than placebo in inducing mucosal healing both at week 8 and at weeks 30 and 54 (ACT 1 week 54 mucosal healing: 18.2% with placebo, 45.5% with 5 mg/kg and 46.7% with 10 mg/kg; $p < 0.001$ for both comparisons with placebo) and in achieving corticosteroid-free remission (ACT 1 week 54: 8.9% with placebo, 25.7% with 5 mg/kg and 16.4% with 10 mg/kg; $p = 0.006$ and p = ns vs placebo, respectively; ACT 2 week 30: 3.3% with placebo, 18.3% with 5 mg/kg and 27.3% with 10 mg/kg; $p = 0.01$ and $p < 0.001$ vs placebo, respectively). Further analysis from ACT 1 and 2 open-label extension phases focused on colectomy and hospitalisation rates during follow-up at 54 weeks. Combined data on all infliximab treated patients demonstrated a colectomy rate of 10% compared with 17% for the placebo treated ones ($p = 0.02$), with an absolute risk reduction of 7% (95% CI 0.01–0.12) in the incidence of colectomy. However, this difference was significant only in the 10 mg/kg group ($p = 0.007$) but not in the 5 mg/kg group ($p = 0.166$), probably reflecting some limitations of the study that hamper a definitive conclusion regarding the dose of infliximab that would have a better colectomy-sparing effect. Finally, infliximab therapy was associated with a 50% reduction in UC-related hospitalisations per 100 patient-years treated ($p = 0.003$ vs placebo) [95].

It is a subject of debate about whether infliximab should be used as monotherapy or in combination with immunosuppressants. Subgroup analysis of ACT trials and data from a single center retrospective study showed no significantly added benefit in patients on concomitant immunosuppressants [96,97]. Moreover, safety concerns about the increased risk of opportunistic infections and the rare hepatosplenic T-cell lymphoma associated with TNF-antagonists/thiopurines combination therapy need for caution about therapeutic strategies [51,98]. In thiopurine-naïve patients, a bridge therapy with infliximab and thiopurines and then thiopurines alone as maintenance may be a reasonable option. These strategies, however, have not yet been tested in UC patients.

Insufficient data currently support the use of adalimumab for moderate-to-severe steroid-refractory or -dependent UC [99,100]. Preliminary data of a multicenter, randomised, double-blind, placebo-controlled study to assess the efficacy of adalimumab for induction of clinical remission in anti-TNFα naïve patients with moderate-to-severe active UC showed a 19.2% rate of clinical remission in the adalimumab (160/80 mg) arm vs a 9.2% rate in the placebo group ($p = 0.021$) [101]. The results suggest the possibility to employ adalimumab in case of intolerance to infliximab, even if adalimumab has still not been approved in the treatment of UC.

In clinical practice a maintenance therapy with infliximab that achieves only response and not steroid-free remission should be carefully evaluated in the face of colectomy, a generally safe and valuable option. There was complete agreement amongst participants about this issue.

In conclusion, infliximab is an effective therapy for induction and maintenance of remission of moderate-to-severe UC refractory to corticosteroids. Maintenance therapy with thiopurines alone after remission with infliximab should be attempted in tiopurine-naïve patients. Trials on steroid-dependent UC patients should be performed. Maintenance therapy with infliximab should be planned as regularly scheduled monotherapy.

7. Induction and maintenance of response/remission in severe steroids refractory Ulcerative Colitis

IG-IBD Statement 7A
Infliximab reduces colectomy rate within 3 months in steroid-refractory severe UC [EL 1b, RG A]. A colectomy is recommended if there is no improvement within 5 days [EL 5, RG D]. Infliximab should be avoided in patients with a complicated disease [EL 5, RG D]. Re-infusions seem more effective than one single infusion to prevent early colectomy [EL 4, RG C], but there is insufficient evidence to provide recommendations on the ideal dosing schedule. Antibiotic prophylaxis against opportunistic infections is suggested [EL 5, RG D]

Severely active UC is an acute clinical condition that may be life threatening and require hospital admission and intensive i.v. corticosteroid treatment [102]. About 30–40% of the patients with severe UC fail to respond to i.v. corticosteroids and require an urgent colectomy. Mortality of severe UC is <1% in specialist centres [103]. The primary endpoint of a rescue therapy is to reduce the urgent colectomy rate or death without significant increase in early post-surgical morbidity. Intravenous cyclosporine A (CyA) is an effective rescue therapy in acute attacks of UC not responding to steroids [104,105] although the use is limited by risks of major toxicity, CyA-related mortality and high rate of relapse after discontinuation [106].

Infliximab has been demonstrated to be effective in patients with moderate-to-severe UC who are refractory to or intolerant to conventional treatment [23]. The role of anti-TNFα agents as a rescue therapy in hospitalised patients with acute attacks of severe UC has been less extensively studied. The first placebo-controlled trial was interrupted because of enrolment difficulties, after recruitment of the first 11 patients [107]. Subsequently, a number of small case series [108–116] has reported positive results.

One randomised placebo-controlled trial has been published with 45 patients hospitalised for severe or moderately severe UC according to the Seo index [117]. Patients were randomised to receive a single infusion of either infliximab 5 mg/kg ($n = 24$) or placebo ($n = 21$) 4 days after initiation of high dose intravenous corticosteroid treatment if they had a fulminant colitis index ≥8 on day 3 or on days 6–8 if they had a Seo index of >150 on days 5–7 [118]. There was a significant reduction in colectomy rates at 90 days with infliximab (RR 0.44, 95% CI 0.22–0.87), with no death occurrence. No significant effect on fulminant colitis and on mucosal healing was demonstrated (RR 2.63, 95% CI 0.59–11.64). Clinical remission was obtained at day 30 in both groups of patients who avoided operation. Two randomised open-label studies [119,120], comparing infliximab to corticosteroids failed to show any significant difference, but the small number of patients raises the possibility of a type II error. Infliximab re-infusions were reported in a number of case series; in one multicentre uncontrolled trial [121], reinfusion seems to be more effective than a single infusion for preventing an early colectomy. No controlled studies have been reported about long-term efficacy in this subset of patients; the little data available from uncontrolled studies is not appraisable for lack of data reference. Although infliximab is reported not to increase post-operative morbidity [118,121], the report of serious infections with two cases of fatal pneumonia [23,121] raises concern for safety in these critically ill patients [1], suggesting an earlier recourse to rescue therapy combined with antibiotic prophylaxis against opportunistic infections.

The efficacy of adalimumab in patients with severe UC remains unknown. One case report [122] and three small case series [99,100,123] have been published showing no benefit in the need of a colectomy in severe UC patients with a lost response or intolerance to infliximab.

8. Anti-TNFα and malignancies

The widespread use of the highly effective immunomodulatory drugs, including the anti-TNFα biologic therapies, is raising concerns about cancer risk, in relation to the physiological role of TNF in cancer suppression. The evidence on the cancer risk associated with the use of anti-TNFα agents in IBD since 1995 has been obtained from the results of clinical trials, meta-analysis, retrospective analysis, case reports, and post-marketing surveillance reports.

IG-IBD Statement 8A
The overall risk of malignancies appears not to be increased in patients treated with anti-TNFα agents [EL 1a]. Their use increases the risk of lymphoma in CD patients with concomitant immunomodulators, although the absolute risk is low [EL 1a]. Combined maintenance treatment with anti-TNFα agents and conventional immunosuppressors is best avoided particularly in young patients because of the risk of hepatosplenic T cell lymphoma (HSTCL) [EL 4, RG C]. Whether a previous history of cancer is a controindication for anti-TNFα therapy is controversial and should be considered on a case-by-case basis [EL 5, RG D]. Conventional screening programs are advisable before the use of anti-TNFα agents [EL 5, RG D]

IG-IBD Statement 8B
Recommendations reported for anti-TNFα agents and malignancies in CD, are also suggested for UC, although the number and follow-up of treated patients are significantly lower than for CD [EL 4, RG C]

8.1. Evidence in CD patients treated with infliximab

A meta-analysis of all randomised controlled trials comparing all anti-TNFα strategies with placebo did not show an increase risk of malignancy in patients receiving anti-TNFα (mean difference vs placebo −0.14% 95% CI −0.4 to 0.2; $p = 0.39$) [43]. These figures are in contrast with the results from a previous meta-analysis including patients with reumathoid arthritis receiving infliximab or adalimumab which reported an increase risk of malignancy (OR 3.29 95% CI 1.19–9.08) [124]. Observational studies (cohort studies and case controls studies) and data from post-marketing surveillance are another relevant source of information. Two recent observational studies from Leuven and Copenhagen did not show any increased risk of malignancy in patients receiving infliximab [54,125]. In an Italian multicentric matched-pair study [126], a comparable frequency of neoplasia was observed in a cohort of 808 infliximab-treated and untreated CD patients matched for clinical variables and followed up from 1999 to 2004 for a median of 25 months (neoplasia; 9 out of 404, 2.22% vs 7 out of 404, 1.73%; $p = 0.40$; OR 1.33, 95% CI 0.46–3.84). No significant differences were also observed when the same cohort of patients was followed up in the long term from 2004 to 2008, for a median follow up of 74 months. The frequency of neoplasia was indeed comparable between the 591 infliximab-treated ($n = 304$) and untreated patients ($n = 287$) still in follow up on 2008 (12 out of 304; 3.94% vs 12 out of 287; 4.19%; $p = 0.95$) [127].

Data from the TREAT Registry reported a comparable rate of malignancies between patients receiving infliximab (3179 patients) and patients receiving other therapies (3111 patients) [128]. A review of studies published from 1995 to 2007, including clinical trials, retrospective analysis and cohort studies showed that the overall frequency of new diagnosed neoplasia in CD patients treated with inflximab was quite low (30/2319; OR 1.29; 95% CI 0.87–1.84) [129].

Although no specific histotypes of cancer appeared associated with Infliximab use in these studies. They also suggested that a small excess lymphoma risk seems to exist in CD patients, although the role of infliximab cannot be currently determined.

More recently, Siegel et al. reported in a meta-analysis involving 8905 patients, that the use of the highly effective anti-TNFα agents with immunomodulators is associated with an increased risk of

NHL in adult CD patients, but the absolute rate of these events is low (SIR 3.23 95% CI 1.5–6.9) [130]. Moreover almost all the patients diagnosed with lymphoma had current or prior exposure to thiopurines and this poses the question whether the major contributors to the increased risk are the innunomodulators or anti-TNFα drugs.

The cancer risk using anti-TNFα agents in CD has recently gained worldwide concern on the basis of the reported development of a rare hepatosplenic T cell lymphoma (HSTC) in 17 young patients (16 CD, 1 UC, 1 rheumatoid arthritis, RA) using concomitant anti-TNFα and conventional ISS drugs, leading to death in 16 [51].

Taken together, these observations suggests that the use of infliximab may increase the risk of lymphoma in CD, particularly in young patients with chronic active, severe disease, with previous or concomitant treatment with conventional ISS. No other specific hystotypes of cancer appeared associated with infliximab use. For these reasons long-term concomitant treatment with anti-TNFα therapies and conventional ISS should be avoided, particularly in young patients. The presence of pre-existing cancer or precancerous lesions should be diagnosed by screening procedures before treating patients with anti-TNFα.

8.2. Evidence in CD patients treated with adalimumab

There is little evidence regarding the cancer risk when using adalimumab in CD. In placebo-controlled trials, a very low cancer incidence (<0.1%) has been reported [14,42,48,82,123,131–135]. This finding appears however related to the signficant lower number of patients currently treated with adalimumab vs infliximab, whilst no direct cause-relationship has been proven between infliximab use and cancer risk in IBD.

8.3. Evidence in UC patients treated with infliximab

There is little evidence regarding the possible cancer risk associated with infliximab use in UC. In 2 large multicenter double-blind placebo-controlled studies (ACT 1 and ACT 2) [23] 3 cases of cancer were diagnosed in 484 patients receiving infliximab (0.61%) and in 1/244 patients receiving placebo (0.40%). These percentages are comparable to the cancer frequency in the general UC population.

A recent review including clinical trials and observational studies conclude that infliximab appears not to increase the risk of cancer in UC (infliximab 3/716 = 0.41% vs placebo 1/265 = 0.37%; p = n.s.) [129]. A relevant issue that needs to be addressed in proper studies is whether dysplasia must be diagnosed before administrating infliximab in UC patients.

8.4. Evidence in UC patients treated with adalimumab

The first two trials using adalimumab in UC was published in 2009, and therefore no conclusive statements can be made regarding the cancer risk using this drug in UC [100,136].

9. Anti-TNFα infections and adverse drug events

The nature and prevalence of adverse drug reactions associated with biologics, reflects the difficulties inherent to the determination of adverse drug events (ADEs). In addition, significant differences in the sources of available safety data limit any detailed comparison. ADE data sources, such as placebo-controlled randomised clinical trials, meta-analysis, case reports, open series, post-approval databases, registries supported by pharmaceutical companies, vary in relation to their strengths. The value of clinical trials data include that patients are prospectively randomised, treatments are standardised and the events are systematically collected allowing better safety comparisons. Such studies are limited, because of the small number of patients and the homogeneous patterns of the subjects. Other limits are, how the medications are administered and whether additional drugs are used. The use of an agent in combination with other medicines is generally controlled in the trial; thus, drug interactions may emerge later. Moreover, for rare ADEs to appear, a large number of patients is required. Post-marketing surveillance through spontaneous adverse events reported to the Food and Drugs administration (MedWatch), periodic safety update reports to EMEA (PSUR) and prospective observational registry (TREAT/ENCORE) takes advantage of a large number of patients which enables uncommon side effects to be detected. So, the inclusion of heterogeneous patient populations with comorbidities and different medical treatments, reflects the clinical practice more accurately. Finally, patients with IBD have an increased risk for infections, related to many other factors, including old age [137], malnutrition, disease severity and a combination with other immunosuppressive drugs [138]. Considered the comparable efficacy of biologics, the appearance of side effects assumes a greater importance in the choice of drug administration. In the absence of trials which compare different types of biologics, it is difficult to identify the different side effects of each anti-TNFα drug. Treatment with biologics is comparatively safe if used for appropriate indications. However, active sepsis is an absolute contraindication [139–142]. All anti-TNFα drugs share similar ADEs, including increased risk of infections from intracellular pathogens like Tuberculosis (TB), other opportunistic infections, autoimmunity, administration reactions, and other infrequent, potential side effects such as neurologic disorders and congestive heart failure [3,142]. It is important to consider the side effects in the context of other IBD therapies, such as corticosteroids and immunosuppressants, which could also increase the risk of infection [98].

10. Infections

IG-IBD Statement 10A
The risk of infections is increased in patients treated with anti-TNFα agents [EL 1]. It is not clear whether this risk is related to biologics or to steroids use, severity of disease and narcotic drugs [EL 3b]. The risk of severe infections is not usually increased [EL 1] but it seems higher in elderly patients [EL 3]. Biologics should not be started during infections [EL 5, RG D]

10.1. Tuberculosis

IG-IBD Statement 10B
Before starting anti-TNFα agents, screening for tuberculosis is mandatory. Appropriate screening includes a full medical history, physical examination, TST or IGRA and a chest X-ray. The IGRA can also be used to distinguish a true positive TST from a false positive TST caused by BCG sensitisation [EL 1, RG A]

IG-IBD Statement 10C
All patients who have a TST result of $\geq$ 5 mm induration or a positive IGRA and planning to receive anti-TNFα agents, should undergo TB chemoprophylaxis [EL 5, RG D]. Patients with a negative TST (< 5 mm) or IGRA should also be treated

for LTBI if there is any evidence, on a chest X-ray, of a remote TB disease or if there is positive history of prior TB exposure [EL 5, RG D]. Patients with a latent TB infection must receive standard therapy with isoniazid for 9 months [EL 3b, RG B]. If active TB is diagnosed, anti-TNFα therapy must be stopped and can be resumed only after TB treatment and specialist consultation [EL 4, RG D]

Post-marketing surveillance amongst patients with rheumatic disease indicates similar rates of TB infections with different anti-TNFα (from 0.01 to 0.05 events per 100 patient-years [3,143].

The clinical pattern of TB amongst patients treated with biologic therapy may be unusual and often includes extrapulmonary severe disease and mortality [144,145]. Many post-biologic tuberculosis, before the current educational programs, occurred early in the treatment [146]. The current rate of TB has shown a sharp decline after the introduction of the educational programs. Before starting biologics, all patients should undergo a detailed medical history. Physical examination should investigate any signs and symptoms that can suspect TB. Before starting therapy, a tuberculin skin test (TST, purified protein derivative, PPD test) and X-rays should be performed. PPD test may show a false negativity related to immunosuppression induced by poor general condition and/or immunosuppressives drugs, including corticosteroids. For patients with a positive PPD test and normal findings on a chest X-ray, treatment of latent TB (LTBI) should be undertaken by a pulmonary specialist [138]. LTBI chemoprophylaxis should be performed with isoniazid for 9 months. Other options should be considered in respect to patient's demographic background, with potential bearing of resistant strains. Anti-TNFα therapy should be delayed for at least 4 weeks after starting chemoprophylaxis. This arbitrary period could be subjected to variability with respect to disease severity. Anergy related to immunosuppressive treatment or previous BCG vaccination may reduce skin testing results [147]. For patients with a negative purified protein derivative test result, interferon-gamma release assay (IGRA) should be considered [138,148]. Specific TB treatment is required for patients with evidence of an active disease. Anti-TNFα therapy must be started or resumed after TB treatment and specialist consultation [138].

10.2. Bacterial and fungal infections

IG-IBD Statement 10D
Anti-TNFα therapy should be temporarily stopped until the resolution of the active bacterial infection [EL 5, RG D]. *Clostridium difficile* infection must be ruled out before starting anti-TNFα therapy [EL 2, RG B]. Patients on immunomodulator therapy have a higher risk of pneumococcal infection [EL 4]. Pneumococcal vaccination is recommended in elderly patients, whereas it is a valuable option in the other age groups on anti-TNFα therapy [EL 5, RG D]

IG-IBD Statement 10E
Consider *Pneumocystis jiroveci* (*P. carinii*) pneumonia prophylaxis in patients treated with anti-TNFα agents who are also receiving other immunosuppressive medications, particularly high-doses of glucocorticoids [EL 4, RG D]

Opportunistic infections have been reported with the use of all TNF inhibitors. Serious infection rates have been reported, ranging from 2.8% to 4% according to randomised controlled trials [12,13,42,48,83].

The observed serious infections in patients treated with anti-TNFα included pneumonia, cellulitis, abscess, skin ulceration and sepsis. In a systematic review of pooled data from 9 clinical trials involving 3,493 patients with rheumatoid arthritis treated with adalimumab or infliximab, it has been found a 2-fold increased risk of serious infection [124]. The TREAT registry (a prospective patient registry of 6273 patients established to study the long-term safety of infliximab and other therapies in CD) showed that infliximab was not an independent predictor of serious infection. Factors independently associated with serious infection included prednisone, narcotic use and moderate-to-severe disease activity [128]. A recent meta-analysis of placebo-controlled trials to evaluate safety and efficacy of anti-TNFα antagonists for Crohn's disease, evaluating 21 studies with 5356 patients, reported that anti-TNFα therapies do not increase the risk of serious infections [43]. Data from the post-marketing experience indicate that opportunistic infections such as nocardiosis, legionella pneumophila, listeria monocytogenes, histoplasmosis, streptococcus pneumonia, parasitic and fungal infections with invasive pulmonary aspergillosis have occurred [138].

Clostridium difficile infection must be ruled out before starting anti-TNFα therapy, considering that IBD patients are at risk of *C. difficile* infection they have an increased need of hospitalisation and an increased mortality rate [138,149].

IBD patients treated with immunosuppressive drugs are at an increased risk of pneumococcal infection [138,150]. Old age and comorbidities are amongst other factors that contribute to increase the risk [137]. Therefore pneumococcal vaccination is recommended in elderly patients whereas it is a valuable option in the other age groups on anti-TNFα therapy.

Cases of Pneumocystis carinii pneumonia (PCP) have been reported amongst patients treated with TNFα inhibitors with an increased hospitalisation and mortality rate [151]. In a case–control study, the risk factor for PCP in patients receiving infliximab included old age, coexisting pulmonary disease and high doses of glucocorticoids [152]. Since the risk of PCP correlates with high-dose glucocorticoid use in some studies, PCP prophylaxis should be considered amongst patients treated with TNFα inhibitors if they are also receiving steroids or other immunosuppressants [153].

10.3. Hepatitis B virus (HBV) infection

IG-IBD Statement 10F
During anti-TNFα therapy there is an increased risk of reactivation in patients with previous and occult HBV infections [EL 4]. Before starting anti-TNFα agents screening for HBV is mandatory [EL 5, RG D]. Appropriate screening includes transaminases, HBsAg and Anti-HBc. If Anti-HBc is positive HBvDna is required [EL 5, RG D]. HBsAg positive patients should be treated with nucleoside analogues [EL 1, RG B]. HBsAg negative patients with positive anti-HBc (+/-anti-HBs) should be carefully monitored during anti-TNFα therapy and nucleos(t)ide analogues started at the appearance of HBsAg and/or HBvDna [EL 4, RG C]

TNFα plays an important role in viral clearance and has a synergistic effect with interferon. Considering that some studies showed steroid-free chemotherapy to be associated with lower risk of HBV reactivation [154], it is conceivable that concomitant steroid or

immunosuppressive treatment (frequent in these patients) enabled virological reactivation.

Reactivation of HBV replication frequently occurs in hepatitis B surface antigen (HBsAg) carriers undergoing immunosuppressive therapy such as steroids and/or chemotherapy. Recently, hepatitis B flare-ups have been described amongst HBsAg carriers treated with anti-TNFα for refractory CD [154–156].

More recently, one case of reactivation of previously occult hepatitis B following infliximab therapy has been reported [157]. According to Esteve et al. [156] and an Italian expert panel opinion [158], anti-TNFα candidate patients should be screened for HBV serum markers. HBsAg positive patients should be given nucleos(t)ide analogues regardless of HBVDNA level. Prophylaxis should be started possibly 4 weeks before anti-TNFα exposure. HBsAg negative patients with positive anti-HBc (+/-anti-HBs) should be carefully monitored during infliximab treatment and nucleos(t)ide analogues initiated at the appearance of HBsAg and HBVDNA (or if anti-HBs became undetectable in previously anti-HBs positive) [158].

10.4. Hepatitis C virus (HCV) infection

IG-IBD Statement 10G
Anti-TNFα agents are safe in patients with HCV infection, although there is little data available [EL 4, RG D]. Active HCV infection should be treated according to a standard therapy practice without stopping biological treatment [EL 5, RG D]

As far as an HCV infection is concerned, there are sporadic reports showing that infliximab does not cause viral reactivation [159]. If an active HCV infection appears during biologic treatment the infection should be treated without stopping anti-TNFα drugs [138].

10.5. Cytomegalovirus (CMV) infection

IG-IBD Statement 10H
Screening for a latent or subclinical CMV infection is not necessary before starting anti-TNFα therapy [EL 2, RG B]. Systemic CMV infection is a contraindication for anti-TNFα therapy; if a systemic infection appears, anti-TNFα must be discontinued and an antiviral therapy should be started [EL 2, RG B]. Before starting treatment or during immunomodulator therapy, in the case of severe colitis with CMV detected in the mucosa and not in the blood, anti-TNFα therapy is not contraindicated [EL 4, RG C]

An association between a CMV infection and a refractory or complicated IBD has been reported [138,160]. Since a subclinical reactivation of latent CMV infection has been frequently associated with concomitant immunosuppressive treatment, it should be necessary to ascertain between a CMV infection and a CMV disease [138]. Data from literature has shown that CMV subclinical reactivation during biological therapy is common, but usually does not influence treatment continuation [138,161,162]. Therefore, screening for a latent or subclinical CMV infection is not necessary before starting biological therapy, considered that only a minority of CMV infections lead to clinical disease [138]. On the other hand, a systemic CMV infection is a contraindication for anti-TNFα therapy; if a systemic infection appears, the use of TNFα inhibitor must be discontinued and an antiviral therapy should be started.

10.6. Varicella zoster virus (VZV) infection

IG-IBD Statement 10I
A previous VZV infection is not a contraindication to anti-TNFα therapy, but biologics should not be started during an active infection with chickenpox or herpes zoster [EL 4, RG D]. In the event of a VZV infection during anti-TNFα therapy, an antiviral treatment should be started [EL 1, RG B] and anti-TNFα agents should be discontinued [EL 5, RG D]. Reintroduction of anti-TNFα therapy is possible after vesicles and fever have been resolved [EL 5, RG D]

Immunosuppressive drugs can increase the risk of a VZV reactivation with appearance of complications such as pneumonia, hepatitis, encephalitis or haemorrhagic disorders [163]. Cases of severe varicella or herpes zoster associated with anti-TNFα therapy in IBD have been reported in patients with IBD, with the need of an antiviral therapy and immunomodulator discontinuation [164].

10.7. Epstein Barr virus (EBV) infection

IG-IBD Statement 10L
Screening for an EBV infection or antiviral prophylaxis before starting anti-TNFα therapy is not justified [EL 2a, RG B]. In the case of a severe EBV infection during biologic therapy, treatment should be interrupted and an antiviral therapy promptly initiated [EL 4, RG D]

A subclinical or self-limited reactivation of latent EBV infection after introduction of immunosuppressive therapy has been reported in IBD [165]. However, it is necessary to underline that also a transient increase of the EBV viral load could be associated with an increased risk of lymphoma, even if, the absolute risk of lymphoma is too low to justify the screening or antiviral prophylaxis before the starting biologics [138]. In the case of severe EBV infection antiviral therapy should be promptly initiated and biologics must be interrupted considering that some cases of death have been reported in patients with CD under immunosuppressive therapy [138,166].

10.8. Influenza virus infection

IG-IBD Statement 10M
Influenza vaccination with inactivated vaccine is an effective strategy before and during anti-TNFα therapy [EL 2, RG B]. The live attenuated vaccine is a contraindication. Early antiviral treatment is recommended when the influenza infection appears during biological therapy [EL 5, RG D]

The incidence of influenza infection in patients with IBD has still not been completely defined. However, immunosuppressive drugs may increase the risk of infection [138,167]. The American Center for Disease Control and Prevention recommend vaccination as the most effective method for preventing influenza virus infection and is therefore recommended for IBD patients on biologics [167]. The live attenuated vaccine is contraindicated [138].

No data is available on the use of antiviral drugs for chemoprophylaxis or treatment of active influenza infection in IBD patients treated with biologics. However, it should be advisable to start an

early antiviral treatment when the infection appears during biological therapy [168].

11. Autoimmunity

IG-IBD Statement 11A
In patients with a lupus like syndrome anti-TNFα therapy should be discontinued [EL 4, RG C]

The appearance of autoantibodies (antinuclear antibodies and autoantibodies to double-stranded DNA: anti-dsDNA) is frequent in patients undergoing anti-TNFα therapy. The reported rates of autoimmunity range from <5% at 6 months amongst certolizumab pegol-treated patients to >50% amongst infliximab-treated patients [3,141,142]. The clinical relevance of autoantibodies is unclear.

If an autoimmune syndrome is suspected the presence of ANAs, anti-dsDNA and extractable nuclear antigens should be checked.

During treatment with anti-TNFα, patients could develop clinical lupus-like symptoms, in this case biologic therapy should be discontinued. It is unclear if the presence of these antibodies will lead to the development of autoimmune diseases in the future [141,142].

A rheumatologist should be consulted in patients with persistent lupus-like symptoms despite withdrawal of anti-TNFα therapy.

In contrast, the development of antibodies against the anti-TNFα does not cause clinical consequences, although occasional lupus-like syndromes have been described [141,169]. There is no indication for monitoring in patients who have no symptoms.

12. Infusion and injection site reactions

IG-IBD Statement 12A
Three-dose induction of infliximab and 8 weeks maintenance dosing reduce drug reactions [EL 1, RG A]. Premedication, 90 minutes before infliximab infusion, may be advisable using diphenildramine (25 to 50 mg), acetaminophen (1 g) and/or steroids [EL 5, RG D]

IG-IBD Statement 12B
Injection site reactions can occur during the first month of adalimumab treatment and can last for 3 to 5 days, but rarely lead to discontinuation of the medication [EL 1]. No premedication is indicated [EL 5, RG D]

Antibodies to infliximab (ATI) may develop in patients receiving infliximab. It was demonstrated that episodic treatment with infliximab is associated with a higher likelihood of developing ATI (30–61%) with respect to the use of maintenance treatment (7–10%) [170]. Moreover, the incidence of ATI was lower in patients receiving immunomodulators (10–43%) than in patients not receiving them (18–75%) [13,83]. It should be stressed that the development of ATI was significantly higher in patients receiving episodic treatment without concurrent use of immunomodulators (38%) than in patients treated with infliximab episodically with accompanying treatment with immunomodulators (16%) [170]. The ACCENT I study found that the presence of ATI was associated with a 12% absolute increase risk of infusion reactions but without an increase in serious infusion reactions or serum-sickness-like reactions [13]. Moreover, another study observed that the occurrence of ATI, in particular, at concentrations greater than 8.0 μg/mL, is associated with an increased risk of infusion reactions and a shorter duration of response [171]. The ACCENT I and ACCENT II studies have shown that the incidence of infusion reactions in patients with ATI increased 2-fold (16–30%) compared to those without ATI (8–16%) [13,83]. It was observed that 3–6% of the 484 patients treated with infliximab in these studies developed ATI.

Infusion reaction rates for infliximab were 17.0% in the ACCENT I trial [13] and 7.1–9.4% in the ACCENT II trial. Serious infusion reaction rates were significantly lower (1.0% and 0.3%, respectively) [83]. The ACT 1 and ACT 2 studies reported the prevalence of infusion reaction was similar in infliximab- and placebo-treated patients: 11% and 9%, respectively [23]. Once an infusion reaction develops, it is recommended to slow or stop the infusion and to treat the patient with diphenhydramine, acetaminophen, antihistamines, and corticosteroids [172].

Subcutaneously administered adalimumab can be associated with injection site reactions, although these are generally less serious in nature. More than 4% of patients in the CHARM trial noted injection site irritation and pain during induction. Injection site reactions were reported in 2% of patients during induction [42].

13. Miscellaneous complications

13.1. Neurologic disorders

IG-IBD Statement 13A
Patients with symptoms of sensory or motor neuropathy should be carefully evaluated and anti-TNFα agents should be stopped if a patient develops demyelinating-like disorders [EL 5, RG D]. Anti-TNFα agents should be used with caution in patients with family histories of multiple sclerosis [EL 5, RG D]

Different neurologic disorders such as optic neuritis, seizure, and new onset or exacerbation of demyelinating disorders, including multiple sclerosis, have been reported with the use of anti-TNFα [173]. The majority of these cases have been reported in association with infliximab use. Neurologic complications have emerged also with adalimumab use. In patients with preexisting or recent onset of central nervous system demyelinating disorders, the benefits and risks of anti-TNFα therapy must be evaluated with caution and to improve safety, patients on biologics and with family histories of multiple sclerosis should be followed up closely in order to identify quickly any abnormal neurological manifestation [3].

13.2. Congestive heart failure

IG-IBD Statement 13B
Infliximab or Adalimumab are formally contraindicated in NYHA III-IV patients [EL 1, RG A]. Anti-TNFα agents should be used with caution in patients with congestive heart failure or decreased left ventricular function (NYHA I–II patients) and therapy should be discontinued if new or worsening symptoms of HF appear [EL 2, RG B]

The results of the ATTACH trial showed that the combined risk of death from different causes of heart failure was significantly increased in the 10 mg/kg infliximab group and adverse events persisted for up to 5 months after stopping therapy [174].

Due to the increased risk of death, it is now recommended that anti-TNFα therapies are formally contraindicated for patients with class III–IV of New York Heart Association (NYHA) congestive heart failure. Caution is required in NYHA I–II patients with low ejection fraction [3,141,142] and echocardiography should be considered and therapy should be discontinued if new or worsening symptoms of heart failure appear [3,141].

13.3. Liver disorders

IG-IBD Statement 13C
If jaundice or ALT elevations >5 times the upper limit appear, anti-TNFα agents should be discontinued [EL 5, RG D]

Elevations in transaminases more frequent in infliximab treated than in placebo treated patients in ATTRACT, ACCENT I and ACCENT II have been reported; 35 cases of liver failure have been reported out of 506,000 patients treated with infliximab [3,141,142]. Reversible cholestatic liver disease has been reported [175,176]. If jaundice or alanine aminotransferase (ALT) elevations >5 times the upper limit anti-TNFα therapy should be discontinued [162].

13.4. Surgery after anti-TNFα

IG-IBD Statement 13D
Whether there is an increased risk of peri or post-operative infections during or after the use of anti-TNFα agents remains controversial [EL 4]. Anti-TNFα agents should be used with caution when surgery is a possible option [EL 5, RG D]

Anti-TNFα therapy can lead to an increased rate of postoperative complications. However, published data report conflicting results [177–179]. The optimal time span between treatment with anti-TNFα and abdominal surgery is unclear. We know that the therapeutic concentrations of these drugs generally persist after infusion for at least 6–8 weeks.

14. Special situations

14.1. Prevention of post-operative recurrence of CD

IG-IBD Statement 14A
Infliximab can be considered in selected high risk patients [EL 2b, RG B] for prevention of post-operative recurrence

CD almost inevitably recurs after surgical resection. The risk of severe endoscopic recurrence is 51% within 1 year, with approximately 7–25% a year risk of symptomatic recurrence and a likelihood of 50% for recurrent symptoms within 5 years after surgery [18,180]. Factors contributing to recurrence include fistulising vs nonfistulising disease, site of disease (ileal vs colonic) and smoking [181–183]. Other risk factors, although not supported by consistent evidence, are youth, previous resection, extent of lesions and type of anastomosis. Prevention of endoscopic recurrence has been advocated. Mesalazine, azathioprine and antibiotics have been shown to be effective in prevention of severe endoscopic recurrence with a rate difference ranging from 10% to 30% [184].

Open-label studies have suggested that infliximab may be beneficial in preventing clinical and endoscopic recurrence [185,186]. In particular, the first report of a small, non-randomised single-center experience, showed that infliximab, combined with low-dose methotrexate was more effective than mesalazine for preventing post-surgical recurrence within 2 years after surgery (100% disease-free vs 25% disease-free) [185].

Subsequently, a small controlled study evaluated the use of infliximab at a dosage of 5 mg/kg at 0, 2, and 6 weeks followed by scheduled maintenance every 8 weeks for 1 year [187]. The rate of endoscopic recurrence at 1 year is significantly lower in the infliximab group (1 of 11 patients; 9.1%) compared with the placebo group (11 of 13 patients; 84.6%, $p = 0.0006$). In contrast, a non-significant higher proportion of patients were in clinical remission in the infliximab group (8 of 10; 80.0%) compared with the placebo group (7 of 13; 53.8%) ($p = 0.38$). Limitations of this study are the small number of patients treated with infliximab, although a statistical significance was achieved, and the very high endoscopic recurrence rate in the control group. Based on this limited evidence the use of infliximab cannot be routinely recommended as a prophylactic treatment. However, in selected patients with high risk factors of recurrence, infliximab may be considered an option. No data is available so far for Adalimumab in this setting.

14.2. Extra-intestinal manifestations (EIMs)

EIMs occur in up to 40% of patients with IBD involving mainly the skin, the joints, and the eyes [188]. They often represent a major therapeutic challenge requiring an aggressive therapy, although community studies suggest that their prevalence and severity might be lower. For those EIMs closely related to IBD activity, treatment usually parallels that of the underlying disease. Differently, treatment is mainly defined on a case-by-case basis since RCTs are lacking.

IG-IBD Statement 14B
In axial and/or peripheral arthritis, in the case of failure of a standard treatment, the use of anti-TNFα agents is suggested [EL 2a, RG B]. Anti-TNFα agents are the treatment of choice in patients with ankylosing spondylitis [EL 1 a RG A]

IG-IBD Statement 14C
An early use of Infliximab [EL 2b] or Adalimumab [EL 4] in Pyoderma Gangrenosum is a valuable option [RG C]

IG-IBD Statement 14D
Anti-TNFα agents (infliximab and adalimumab) can be considered in resistant cases of uveitis [EL 4, RG C]

Articular manifestations are usually defined as peripheral and axial arthritis and occur in 7% up to 25% of patients [188]. The former is also sub-classified as Type I (pauci-articular mainly large weight bearing joints) and Type II (poly-articular small joints). Axial arthritis (AS) includes spondylitis and sacroiliitis [189]. In Type I peripheral arthritis the emphasis should be on the treatment of the underlying IBD, including corticosteroids, immunomodu-

lators, and eventually anti-TNFα agents. In the case of failure of traditional therapy (salazopyrin, methotrexate, physioterapy) the efficacy of anti-TNFα agents is largely established [190,191], with obvious advantage for patients with an intestinal active disease. A large, prospective, open-label trial demonstrated improvement of peripheral arthritis in IBD patients who had previously been refractory to corticosteroids, 6-MP, azathioprine, or methotrexate. In this study, patients were treated with infliximab 5 mg/kg at 0 (luminal CD) or 0, 2, and 6 (fistulising CD) weeks. At the end of 12 weeks, 36/59 (61%) patients had significant improvement of their arthritis, defined by improvement of 1 point in the arthritis component of the CD activity index (CDAI) score, and complete resolution of arthritis in 27/59 (46%) patients [192].

AS does not always parallel intestinal inflammation and may progress independently of IBD. There are several controlled studies demonstrating the efficacy of infliximab and adalimumab for AS, but the coexistence of IBD is not reported [193–195]. Also small uncontrolled series support the use of Infliximab in IBD associated axial arthritis [196,197]. To date, there are no trials which specifically examinin the efficacy of adalimumab for patients with concomitant IBD and articular manifestations.

Cutaneous manifestations such as erythema nodosum (EN) and pyoderma gangrenosum (PG) are classically associated with IBD, presenting in 3–20%, and 0.5–20% of patients, respectively [198]. PG is a much more severe, and sometimes debilitating, skin condition than EN. Oral corticosteroids, cyclosporine and tacrolimus have been used with variable results [198,199].

Several case reports on the benefit of using anti-TNFα agents (mainly infliximab) in the treatment of cutaneous vasculitis are available. In many cases PG refractory to standard medications (oral, intravenous, and intralesional corticosteroids; azathioprine; 6-MP; antibiotics; dapsone; cyclosporine, FK506, and mycophenolate) have been successfully treated with anti-TNFα agents. In only one small multicenter, randomised, placebo-controlled trial (30 patients with PG, 19 of whom also had IBD) infliximab 5 mg/kg as a single infusion has been compared with placebo [200]. A response has been observed in 46% of patients compared to 6% of those receiving placebo ($p = 0.0025$). Only single case reports are available addressing the use of anti-TNFα medications for erythema nodosum and more rare mucocutaneous EIM such as refractory EN, Sweet's syndrome and metastatic cutaneous CD [201].

Ocular manifestations develop in 2–6% of IBD patients with the most common being episcleritis and uveitis [198]. Many case reports and pilot studies demonstrate that infliximab and adalimumab can suppress uveitis and scleritis associated with various autoimmune disorders including IBD. Unfortunately, however, no RCTs have been undertaken. In addition, paradoxical appearance of uveitis during infliximab therapy has also been reported [202].

14.3. Refractory pouchitis

IG-IBD Statement 14E
Use of infliximab or adalimumab is an option for refractory pouchitis [EL 4, RG C]

Pouchitis is an idiopathic chronic inflammatory condition that may occur in the ileal pouch in up to 60% of patients after proctocolectomy and ileo-pouch-anal anastomosis (IPAA) for UC [203]. Extensive colitis, extra-intestinal manifestations, being a non-smoker, p-ANCA positive serology, and non-steroidal anti-inflammatory drug use are possible risk factors [204]. Approximately 10–15% of patients with acute pouchitis develop chronic pouchitis. Chronic pouchitis may also became antibiotic-refractory, very difficult to treat, and lead to pouch failure. A small number of cases addressing the efficacy of infliximab and adulimumab in chronic refractory pouchitis have been published. In the last years a number of case reports [205] or small pilot studies using anti-TNFα agents have been reported. In a single-blind prospective cohort study, 10 patients with chronic pouchitis and ileitis were treated with infliximab 0.5 mg/kg at 0, 2, and 6 weeks [206]. All patients had a previous diagnosis of UC but curiously all presented minor and even major lesions in the small bowel detected by capsule endoscopy. At the end of therapy, 9 out of 10 patients were in clinical remission and 8 out of 10 achieved endoscopic remission. Similarly, a clinical response was obtained at 10 weeks in 22/25 patients with refractory pouchitis and 6/7 patients with pouch fistula [207]. In an open-label study 17 patients with CD and active inflammation of the pouch who failed to conventional therapy have been treated with adalimumab with 160/80 mg regimen and 40 mg weekly. After 8 weeks eight patients (47.1%) had a complete symptom response and 4 (23.5%) had a partial response [208].

15. Anti-TNFα therapy and pregnancy

IBD occurs frequently during the peak reproductive years. An understanding of the safest management strategies of IBD during pregnancy and breastfeeding is crucial to the health of both the mother and child. Unfortunately, data on the safety of medications in these clinical settings is limited and often the information is contradictory. The United States Food and Drug Administration (FDA) classification of drugs offers a guide to the use of medications during pregnancy [209]. The immunomodulators are the most controversial agents used in the treatment of the pregnant woman with IBD. In particular the use of biologic medications during the conception period and pregnancy is a cause of great concern for patients and physicians. Anti-TNFα therapies are considered category B drugs for pregnancy. To date, there is no evidence that TNFα antagonists are associated with embryo toxicity, teratogenicity or increased pregnancy loss. However, caution should be taken when anti-TNFα agents are used during pregnancy, as experience in humans, with regard to safety for the developing foetus, is still limited. The information presented here must be individualized to the specific situation of each patient, their acceptance of risk, and their degree of disease severity.

IG-IBD Statement 15A
Women of child-bearing age should be advised to avoid becoming pregnant during anti-TNFα therapy [EL 5, RG D]. If anti-TNFα therapy is necessary to control disease activity during pregnancy, the benefits of treatment outweigh the risks particularly during the first two trimesters of pregnancy [EL 4, RG C]

15.1. Infliximab

The use of infliximab during pregnancy and prior to conception is restricted. Recent data shows that infliximab administration during pregnancy appears to be safe.

Infliximab is an IgG1 antibody, which does not cross the placenta in the first trimester. Whilst this protects the infant from exposure during the crucial period of organogenesis, infliximab crosses the placenta in the third trimester [210]. However the effects of anti-TNFα on the immune system of the foetus and the long-term effects on the developing infant are not known.

Animal studies using analogous anti-TNFα agents have not shown any evidence of teratogenicity and adverse pregnancy or maternal outcome [211]. The maximum dose of monoclonal antibody used was 40 mg/kg (usual dose of infliximab is 5 mg/kg).

There is a growing body of evidence that suggests that the risk by using infliximab during pregnancy is low.

The two largest studies considering the safety of infliximab during pregnancy are from the TREAT Registry [212] and the Infliximab Safety Database [213]. Patients may or may not have been treated with infliximab for entry. Of the 5807 patients enrolled, 66 pregnancies were reported, 36 with prior infliximab exposure. Foetal malformations did not occur in any of the pregnancies. The rates of miscarriage (11.1% vs 7.1%; $p < 0.53$) and neonatal complications (8.3% vs 7.1%; $p = 0.78$) were not significantly different between infliximab-treated and infliximab naïve patients, respectively.

The Infliximab Safety Database is a retrospective data collection instrument. Pregnancy outcome data is available for 96 women with direct exposure to infliximab [213]. This was primarily exposure during conception and the first trimester. The 96 pregnancies resulted in 100 births. The expected vs observed outcomes amongst women exposed to infliximab were not different from those of the general population.

A series of 10 women with intentional maintenance infliximab use throughout pregnancy was also reported [214]. All 10 pregnancies ended in live births, with no reported congenital malformations.

Infliximab crosses the placenta preferentially in the third trimester and is detectable in the infant for several months after birth. Discontinuing infliximab early in the third trimester has been considered to decrease transport across the placenta in the third trimester and thereby decrease levels in the newborn. It can then be resumed immediately after delivery. If the mother flares during this time she can receive her appropriate dose of infliximab, although some argue that management with corticosteroids should be considered for this short period.

There is no available data on the use of infliximab during breast feeding except that some case reports suggest placental rather than breast milk transfer of infliximab. From a few data available the use of infliximab is probably compatible.

15.2. Adalimumab

Adalimumab is a pregnancy category B drug. Limited data addressing the safety of Adalimumab during pregnancy is available. OTIS (Organization for Teratology Information Specialists) reports about women enrolled in a prospective study of adalimumab in pregnancy and an additional adalimumab exposed pregnant women in a registry [215].

The rate of spontaneous abortion and stillbirth was similar in patients and controls. The rates of congenital malformation and preterm delivery are also within the expected range.

Adalimumab, an IGg1 antibody, would be expected to cross the placenta in the third trimester as infliximab does. However, the benefit or harm of this to the mother or foetus is unknown.

There have been no known reports to date for adalimumab use during lactation. Since it is unknown whether adalimumab is excreted in human milk or absorbed systemically after ingestion, and whether potential adverse reactions can occur in the nursing infants, the use of the drug during nursing depends on the importance of the drug to the mother. In general, the drug is continued during breastfeeding. Adalimumab levels have not been available to measure in breast milk.

Conflict of interest

None declared.

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Appendix A. Contributing experts to the Consensus meeting

Luciano Alessandroni (Rome), Maria Cappello (Palermo), Michele Comberlato (Bolzano), Silvio Danese (Milan), Marco Daperno (Turin), Ferdinando Ficari (Florence), Giuseppe Frieri (L'Aquila), Walter Fries (Messina), Gianmichele Meucci (Milan), Monica Milla (Florence), Gabriele Riegler (Naples), Dario Sorrentino (Udine), Piero Vernia (Rome), Giorgio Zoli (Cento).

Representative of the Italian Association of Patients (AMICI): Salvo Leone.

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