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Guidelines

Use of biologics for the management of Crohn's disease: IG-IBD clinical guidelines based on the GRADE methodology

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ABSTRACT

A cure for Crohn's disease (CD), a chronic inflammatory disease of the gastrointestinal tract of unknown etiology, is not available, so patients require lifelong management to keep inflammation under control. The therapeutic armamentarium has expanded with approval of several biological drugs, including infliximab, adalimumab, vedolizumab and ustekinumab – monoclonal antibodies that target different inflammatory pathways – and darvadstrocel, a suspension of expanded human allogeneic, adipose-derived, mesenchymal stromal cells for the treatment of refractory complex perianal fistula. Notwithstanding existing practice guidelines on medical therapy for CD, the Italian Group for the Study of Inflammatory Bowel Disease felt the need to issue new guidelines focused on the use of biologics for managing the intestinal manifestations of CD and based on the GRADE methodology. This document presents recommendations regarding six clinical settings, from the induction to the maintenance of clinical remission, and from optimization and de-escalation of treatments to dealing with perianal CD and post-operative recurrence. The 19 evidence-based statements are supported by information on the quality of the evidence, agreement rate among panel members, and panel comments mainly based on evidence from real world studies.

1. Introduction

Crohn's disease (CD) is a progressive, inflammatory condition of the gastrointestinal tract [1]. It often requires continuous medical treatment, as the etiology of the disease is unknown and, therefore, a curative therapy is not available [1]. Furthermore, the degree of patients' symptoms does not always match the inflammatory activity, and subclinical or overt inflammation is able to cause the well-known complications of the disease (i.e., strictures,

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fistulas, abscesses). Over the years, these complications can lead to progressive bowel damage and the need for repeated surgery, with the consequent risks of short bowel and a permanent stoma [2,3]. Thus, there are important unmet needs in the management of CD.

CD management has benefitted by the increased knowledge over the past 20 years of the immunological mechanisms involved in the pathogenesis of the disease. This knowledge has led to the introduction of several biological therapies, monoclonal antibodies that selectively block key mediators of inflammation. For several years, the most advanced therapies for patients with moderate-to-severe CD involved blocking the activity of tumor necrosis factor (TNF) [4]. Infliximab was the first anti-TNF monoclonal antibody approved by the European Medicines Agency (EMA) for the treatment of CD, in 1999, and it was followed by adalimumab in 2007. Later, other biologics with different mechanisms of action became available for treating CD in clinical practice. Vedolizumab – a gut-selective inhibitor of $\alpha_4\beta_7$ integrin [5] – has been approved by EMA in 2014. Ustekinumab – an inhibitor of subunit p40 of interleukins 12 and 23 [6] – obtained approval by EMA in 2016. Finally, a recently approved therapy for refractory complex perianal CD is darvadstrocel, a preparation of human mesenchymal stem cells expanded from adult adipose tissue and designed for intralesional use during surgery for perianal disease [7].

In this evolving scenario, the American Gastroenterological Association [8] and the European Crohn's and Colitis organisation [9] have recently published clinical practice guidelines on the use of therapeutics in CD. However, both documents took a broad view not limited to the use of biologics, which is the focus of the present guidelines. Furthermore, because economic and legal issues, as well as different viewpoints in general, may influence the indications for biologics, we believe that additional national recommendations are necessary to complement the existing international guidelines.

In 2019, the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) began a project to develop clinical guidelines, starting with the use of biologics and small molecule drugs in ulcerative colitis [10,11]. The current document presents the official recommendations on the use of biologics for managing CD. It deals with intestinal outcomes and does not provide indications for treating extra-intestinal manifestations, which will be the focus of a separate paper. These guidelines were developed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, which has become the reference method for developing high-quality, evidence-based recommendations for clinical practice [12]. They are accompanied by a technical review [13] that provides a detailed analysis of the evidence on which these recommendations are based. The work was fully funded by IG-IBD and did not receive any external funding.

2. Methods

2.1. Consensus process for guideline development

The steps used by IG-IBD for guideline development (Fig. 1) were extensively described in our previous clinical guidelines on the use of biologics and small molecule drugs in ulcerative colitis [10,11]. Briefly, to involve as many Italian IBD experts as possible in different tasks, we created the following work groups: (i) a *steering committee* that coordinated and promoted the project (six IG-IBD members); (ii) a *working panel* that was involved in the various rounds of voting and revising the statements (25 IG-IBD members and two representatives of patients' associations); (iii) a *methodology panel* that did the systematic literature search, summarized the evidence according to the GRADE approach, and drafted the technical review (three non-IG-IBD members); and (iv) a *review panel* of 19 IG-IBD members who offered their opinions on late drafts of the manuscript.

The steering committee established six main clinical settings to be assessed during guideline development (for each setting, the corresponding critical outcomes are stated):

- *Setting 1*: Induction of remission in adults with moderate-to-severe CD (critical outcomes: clinical remission, clinical response, mucosal healing, and serious adverse events - SAEs). This setting was divided into four sub-settings:
  - 1A: Biologics vs. no treatment in biologic-naïve patients
  - 1B: Comparisons among drugs in biologic-naïve patients
  - 1C: Biologics vs. no treatment in biologic-experienced patients
  - 1D: Comparisons among drugs in biologic-experienced patients.
- *Setting 2*: Anti-TNF-based combination therapy for the induction of remission in adults with moderate-to-severe CD (critical outcomes: clinical remission, clinical response, mucosal healing, and SAEs).
- *Setting 3*: Maintenance of remission induced by biologics (critical outcomes: clinical remission, mucosal healing, and SAEs).
- *Setting 4*: Optimization strategies and de-escalation of anti-TNF-based treatments (critical outcomes: clinical remission, mucosal healing, and SAEs).
- *Setting 5*: Complex perianal CD (critical outcomes: achievement of fistula healing/closure, maintenance of fistula healing/closure, and SAEs).
- *Setting 6*: Prevention of post-operative recurrence of CD (maintenance of endoscopic remission, clinical remission, and SAEs).

2.2. Grading of the evidence and strength of the recommendations

The quality of the evidence and strength of the recommendations were evaluated according to the GRADE approach [12]. For each statement (or part of the statement) the quality of evidence was classified as high, moderate, low, very low, or knowledge gap (Table 1). Details on the process of grading the evidence and evaluating the overall quality of evidence for each clinical question are provided in the technical review [13].

The strength of each recommendation was defined as strong ("IG-IBD recommends…") or conditional ("IG-IBD suggests…"). Interpretations of the different strengths of recommendation for patients and clinicians are provided in Table 2. In line with the GRADE approach, the strength of each recommendation arose from four components: risk–benefit balance, patients' values and preferences, costs and resource allocation, and quality of evidence. There were three situations in which no recommendation was made ("IG-IBD makes no recommendation…"): (a) when the confidence in the effect estimates was so low that IG-IBD felt that a recommendation would be too speculative; (b) when the balance between desirable and undesirable outcomes was very close, and the values and preferences were not known or variable; and (c) when there was no evidence to make a recommendation (i.e. knowledge gap).

Overall, three pieces of information are provided to help readers to fully evaluate each statement: (i) strength of the recommendation, (ii) quality of the evidence, and (iii) agreement rate (i.e. the percentage of the members of the working panel who agreed on the final statement). It should be noted that the agreement rate was not considered for the approval or the rejection of a draft recommendation, as the rates are just an additional tool for assessing the validity of the statements. In addition, the need to conceptually overcome in some points intrinsic limitations of the GRADE methodology emerged during the drafting of these guidelines. Therefore, the statements were integrated – when necessary

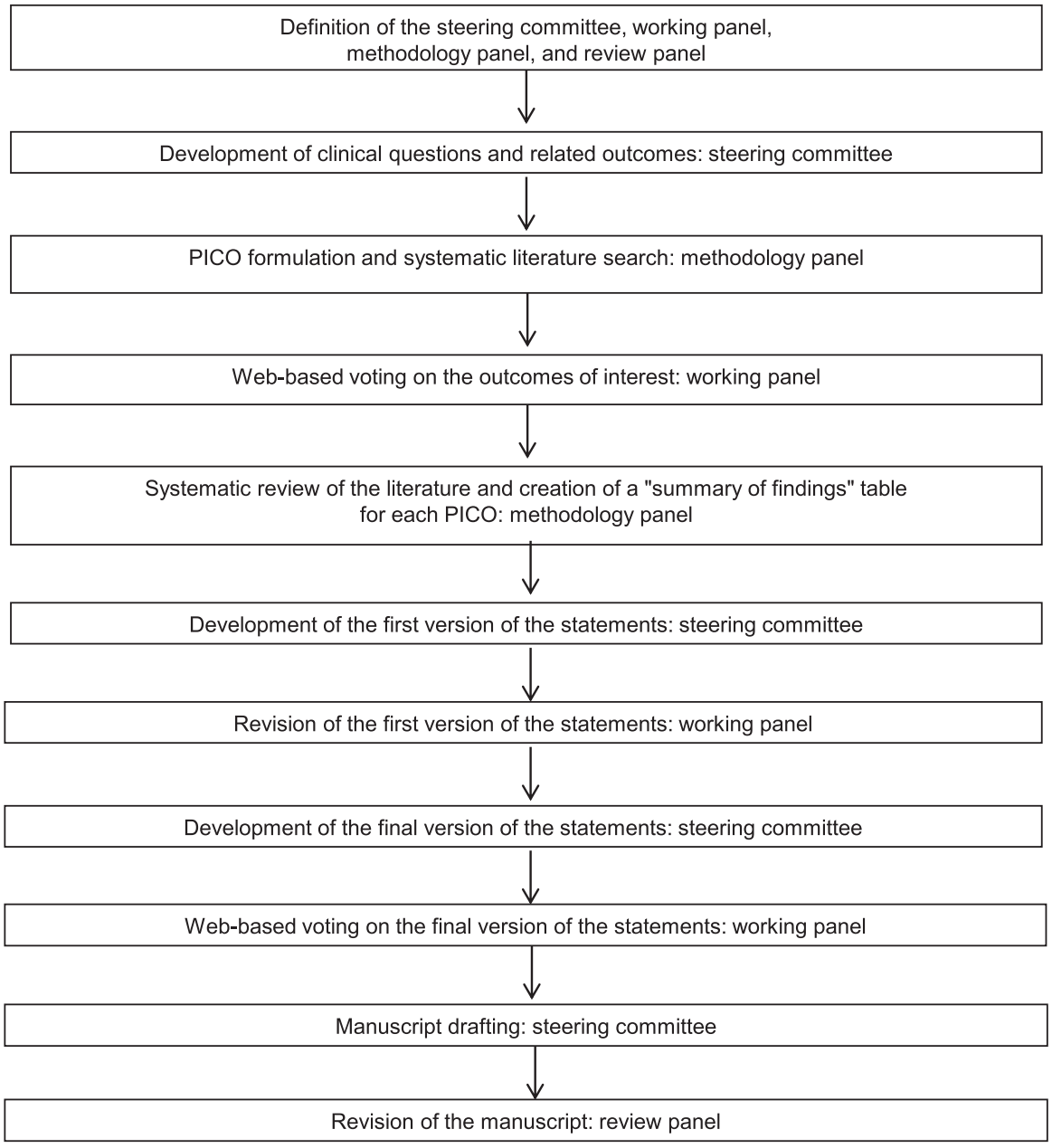

Fig. 1. Guideline development process.

Table 1
GRADE definitions of the quality of the evidence. Modified from [12].

Quality of evidence	Interpretation
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect (even if it is possible that the true effect is different).
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be different from the estimate of effect.
Knowledge gap	There is insufficient evidence to determine the true effect.

Table 2
GRADE interpretations of the strength of the recommendations. Modified from [12].

Strength of recommendation	For patients	For clinicians
Strong "IG-IBD recommends"	Most individuals in this situation would want the recommended course, and only a small proportion would not.	Most individuals should receive the recommended course of action.
Conditional "IG-IBD suggests"	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices will be appropriate for different patients.
No recommendation "IG-IBD makes no recommendation"	–	The confidence in the effect estimate is so low that any effect estimate is speculative.

- by panel comments, which were mainly based on real-world evidence and/or expert opinions.

3. Setting 1: induction of remission in adults with moderate-to-severe CD

3.1. Biologics vs. no treatment in biologic-naïve patients

Statement 1: For adults with moderate-to-severe CD refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, vedolizumab or ustekinumab to induce remission. (*Strong recommendation. Moderate-quality evidence for infliximab, adalimumab and vedolizumab; very low-quality evidence for ustekinumab. Agreement rate: 100%*)

To induce remission of moderate-to-severe CD that is refractory to conventional therapy in adults who are naïve to biologics, IG-IBD recommends using any of the four biologics currently available for CD. They are all effective in this setting, even if the quality of evidence is not the same.

Regarding infliximab, the recommendation is based on a review of the literature (see PICO 01 of the technical review) that showed its clear superiority to placebo for inducing clinical remission (risk ratio [RR], 1.95; 95% confidence interval [CI], 1.59–2.40) and mucosal healing (RR, 2.66; 95% CI, 1.66–4.27). In contrast, infliximab was not found to be superior to placebo for inducing a clinical response (RR, 2.14; 95% CI, 0.91–5.03). Regarding safety outcomes, there were no differences between infliximab and placebo for the risks of adverse events (AEs) (RR, 1.01; 95% CI, 0.94–1.08) and SAEs (RR, 0.77; 95% CI, 0.51–1.17). The overall quality of the evidence was moderate due to serious inconsistency (high heterogeneity of the data on clinical response) and imprecision (scarce data on mucosal healing).

Similar findings were observed for adalimumab (PICO 02). Based on data from three studies that assessed efficacy at 4 weeks and from eight studies that evaluated safety at 4–56 weeks, adalimumab was superior to placebo for inducing clinical remission (RR, 3.60; 95% CI, 2.19–5.92) and clinical response (RR, 2.13; 95% CI, 1.44–3.16). Evidence was also sought for mucosal healing, but data were insufficient to draw conclusions. Furthermore, adalimumab posed a lower risk of SAEs compared to placebo (RR, 0.59; 95% CI, 0.40–0.86). The quality of the evidence for adalimumab was moderate (as it was for infliximab), mainly due to serious imprecision (sparse data) on clinical remission.

Panel comment beyond GRADE: Biosimilars of infliximab and adalimumab have equivalent efficacy/effectiveness and safety to the originator products [14–16] and cost less than the originator products. Their availability reinforces our recommendation to use these two drugs as first-line biologics in most patients. We expect to be able to make a similar recommendation for vedolizumab and ustekinumab when low-cost biosimilars for these two drugs become available.

The recommendation to use vedolizumab to induce remission in adults naïve to biologics is based on three studies that assessed efficacy at 6 weeks and on five studies with safety data at 6–46 weeks (PICO 07). These studies showed that vedolizumab is superior to placebo for inducing clinical remission (RR, 2.18; 95% CI, 1.29–3.69) and clinical response (RR, 1.47; 95% CI, 1.07–2.03), while there were no differences between vedolizumab and placebo on risks of AEs (RR, 1.01; 95% CI, 0.95–1.09) and SAEs (RR, 1.04; 95% CI, 0.75–1.44). Data were insufficient regarding mucosal healing. The quality of the evidence was moderate due to serious imprecision (sparse data) on clinical remission.

Evidence on the efficacy of ustekinumab for inducing remission in biologic-naïve CD patients comes from only one study that assessed efficacy at 8 weeks, while five studies reported on safety at 8–44 weeks (PICO 09). The overall quality of evidence was judged to be very low due to very serious imprecision (sparse data and wide CI) for mucosal healing and to serious indirectness for clinical remission (approximately 30% of the tested population had previously received anti-TNF agents). The data, however, showed that ustekinumab was clearly superior to placebo for inducing clinical remission (RR, 2.06; 95% CI, 1.49–2.84) and clinical response (RR, 1.73; 95% CI, 1.30–2.29), while there was no difference for mucosal healing (RR, 1.89; 95% CI, 0.64–5.56). Finally, there were similar risks of AEs (RR, 0.96; 95% CI, 0.90–1.02) and SAEs (RR, 0.79; 95% CI, 0.56–1.11) between ustekinumab and placebo.

Panel comment beyond GRADE: Most studies investigated vedolizumab and ustekinumab as second-line agents. Nonetheless, recent studies demonstrated the effectiveness of these drugs also in patients who were naïve to biologics [17–20].

3.2. Comparisons among drugs in biologic-naïve patients

Statement 2: For adults with moderate-to-severe active CD, refractory to conventional therapy, who are naïve to biologics, IG-IBD makes no recommendation on the preferential use of:
- **infliximab over adalimumab, vedolizumab, or ustekinumab**
- **adalimumab over vedolizumab or ustekinumab, or**
- **vedolizumab over ustekinumab**

(*No recommendation. Very low-quality evidence for all comparisons, except for moderate-quality evidence for the comparison between adalimumab and ustekinumab. Agreement rate: 88%*)

In the choice between infliximab and adalimumab for moderate-to-severe CD, refractory to conventional therapy, in patients who are naïve to biologics, evidence came from indirect treatment comparisons. Literature review (PICO 05) revealed several methodological concerns, including serious inconsistency for clinical response and AEs, and serious imprecision for SAEs (sparse data). Thus, there was very low-quality evidence overall. Adalimumab was superior to infliximab – although with a wide CI – for inducing clinical remission (RR, 0.54; 95% CI, 0.32–0.93), but the two biologics were comparable in achieving clinical response (RR, 1.01; 95% CI, 0.39–2.57). They also posed similar risks of AEs (RR, 1.04; 95% CI, 0.92–1.18) and SAEs (RR, 1.31; 95% CI, 0.74–2.30). However, the data were insufficient to draw a conclusion about mucosal healing. Given all the aforementioned methodological issues, and the lack of difference between the two biologics as maintenance treatment for all considered outcomes (PICO 22), IG-IBD decided to make no recommendation on a preferential use of infliximab or adalimumab despite the reported superiority of adalimumab in achieving clinical remission at induction.

Panel comment beyond GRADE: Several large, real-world studies have highlighted the substantial equality in effectiveness between infliximab and adalimumab for CD patients who are naïve to biologics [21–25].

Methodological concerns resulted in a very low overall quality of evidence for the comparisons between infliximab and vedolizumab (PICO 11) and between infliximab and ustekinumab (PICO 12). No difference between infliximab and vedolizumab was observed for critical outcomes including clinical remission (RR, 0.89; 95% CI, 0.51–1.57), clinical response (RR, 1.46; 95% CI, 0.58–

3.63), and SAEs (RR, 0.74; 95% CI, 0.44–1.26), while data were insufficient for mucosal healing. In the comparison between infliximab and ustekinumab, no differences were detected for all critical outcomes, namely clinical remission (RR, 0.95; 95% CI, 0.65–1.39), clinical response (RR, 1.24; 95% CI, 0.50–3.04), mucosal healing (RR, 1.41; 95% CI, 0.43–4.58), and SAEs (RR, 0.98; 95% CI, 0.57–1.67). Similarly, no difference was observed for all outcomes between infliximab and vedolizumab (PICO 23), as well as between infliximab and ustekinumab (PICO 24) in the maintenance setting.

In the choice between adalimumab and vedolizumab for moderate-to-severe CD, in patients who are naïve to biologics, the evidence came from indirect treatment comparisons and was affected by serious or very serious imprecision for all critical outcomes. As a result, the overall quality of evidence was very low (PICO 13). In addition, no differences were observed for efficacy outcomes including clinical remission (RR, 1.65; 95% CI, 0.80–3.40) and clinical response (RR, 1.45; 95% CI, 0.87–2.41), while data were insufficient for mucosal healing. A reduced risk of SAEs was detected for adalimumab compared to vedolizumab (RR, 0.57; 95% CI, 0.34–0.94). Similarly, no difference in all efficacy outcomes was observed at maintenance between the two drugs (PICO 25).

Panel comment beyond GRADE: Real-world evidence has demonstrated a similar effectiveness between adalimumab and vedolizumab in CD patients, both naïve and experienced to biologics [26].

Differently from all the other comparisons, the evidence on the choice between adalimumab and ustekinumab came from a direct comparison (the SEAVUE study). At the time of drafting of this manuscript, this study had only been reported in a conference abstract, precluding full critical appraisal. The overall quality of evidence was moderate (PICO 14). No difference was detected for efficacy outcomes including clinical remission (RR, 1.05; 95% CI, 0.89–1.24) and clinical response (RR, 0.99; 95% CI, 0.87–1.11), while data were insufficient for mucosal healing. Furthermore, no difference was reported for SAEs (RR, 1.25; 95% CI, 0.77–2.03), and the comparison of the two drugs as maintenance therapy did not show any difference (PICO 26).

Finally, for the comparison between vedolizumab and ustekinumab in biologic-naïve patients (PICO 46), very low-quality evidence was found (indirect treatment comparisons, serious imprecision for critical outcomes). No differences were found at induction between the drugs regarding clinical remission (RR, 1.06; 95% CI, 0.57–1.96), clinical response (RR, 0.85; 95% CI, 0.55–1.30), AEs (RR, 1.05; 95% CI, 0.96–1.16), or SAEs (RR, 1.32; 95% CI, 0.82–2.11), while data were insufficient for mucosal healing. Similarly, no difference was detected between the two drugs used as maintenance therapies (PICO 27).

3.3. Biologics vs. no treatment in biologic-experienced patients

Statement 3: For adults with moderate-to-severe CD refractory to a previous therapy with adalimumab, IG-IBD makes no recommendation in favor of or against using infliximab to induce remission. (*No recommendation. Knowledge gap. Agreement rate: 64%*)

There is insufficient evidence to inform this specific question. Therefore, IG-IBD is unable to make recommendations on the use of infliximab for the induction of remission in patients previously found to be refractory to a different anti-TNF agent (PICO 03).

Panel comment beyond GRADE: We could not address this clinical question using evidence from randomized controlled trials. Nonetheless, 20 years of clinical experience with infliximab and a demonstrated efficacy in observational studies [25,27] suggest that it is effective also in patients in whom previous treatment with adalimumab was unsuccessful. This point is reinforced by the efficacy of the other anti-TNF agent - adalimumab – in this setting (see below). However, it should be noted that the current availability of several biologics with different mechanisms of action makes clinicians quite reluctant to switch from one anti-TNF agent to another, particularly in cases of primary nonresponse. Conversely, a switch from one anti-TNF agent to another should be considered when an effective anti-TNF agent must be withdrawn due to intolerance [28].

Statement 4: For adults with moderate-to-severe CD refractory to at least one biologic, IG-IBD recommends using adalimumab, vedolizumab or ustekinumab to induce remission. (*Strong recommendation. Moderate-quality evidence for adalimumab and vedolizumab, very low-quality evidence for ustekinumab. Agreement rate: 80%*)

IG-IBD recommends using adalimumab, vedolizumab or ustekinumab in adults with moderate-to-severe CD refractory to at least one biologic. These three drugs are all effective in this setting, even if the quality of the evidence and the motivations underlying this recommendation differ between drugs.

Regarding adalimumab, the evidence comes from two studies with data on clinical remission and clinical response at 4 weeks and from eight studies with data on AEs and SAEs at 4–56 weeks (PICO 04). Of note, PICO 04 specifically refers to patients previously treated with an anti-TNF agent. About efficacy, evidence was in favor of adalimumab over placebo for the outcomes of clinical remission (RR, 3.00; 95% CI, 1.65–5.42) and clinical response (RR, 1.54; 95% CI, 1.20–1.97), while data were insufficient for the assessment of mucosal healing. Notably, adalimumab also had a better safety profile than placebo for SAEs (RR, 0.59; 95% CI, 0.40–0.86). The overall quality of evidence was moderate due to serious imprecision (sparse data) for clinical remission.

Panel comment beyond GRADE: See the aforementioned comments on the current utility of switching from one anti-TNF agent to another.

The recommendation to use vedolizumab to induce remission in adults with moderate-to-severe CD refractory to at least one biologic is based on three studies that assessed efficacy at 6 weeks and five studies with data on safety at 6–46 weeks (PICO 08). Vedolizumab was superior to placebo for the induction of one critical outcome, i.e. clinical response (RR, 1.51; 95% CI, 1.01–2.25), while there were no differences between vedolizumab and placebo on clinical remission (RR, 1.25; 95% CI, 0.62–2.53), risk of AEs (RR, 1.01; 95% CI, 0.95–1.09) and risk of SAEs (RR, 1.04; 95% CI, 0.75–1.44). Data were insufficient regarding mucosal healing. The quality of the evidence was moderate due to serious imprecision for the outcome clinical remission (sparse data).

Panel comment beyond GRADE: Vedolizumab has been shown to be effective and safe in patients with CD [5], and it has frequently been administered as a second-line biologic in clinical practice. Consequently, despite the drug being superior to placebo only for clinical response (a critical outcome), IG-IBD decided to give a strong recommendation for vedolizumab.

Regarding ustekinumab, the overall quality of evidence was very low due to very serious imprecision (sparse data) and serious indirectness on mucosal healing (PICO 10). Nonetheless, the recommendation made is strong due to the superiority of ustekinumab to placebo for inducing clinical remission (RR, 2.29; 95% CI, 1.40–3.76) and clinical response (RR, 1.77; 95% CI, 1.39–2.26). In contrast, there were no differences for mucosal healing (RR, 4.24;

95% CI, 0.15–123.1) and for the risks of AEs (RR, 0.96; 95% CI, 0.90–1.02) and SAEs (RR, 0.79; 95% CI, 0.56–1.11).

Panel comment beyond GRADE: Similarly to vedolizumab, ustekinumab has been used in clinical practice mostly in patients who were previously exposed to another biologic. The drug demonstrated clear effectiveness in this setting [29].

3.4. Comparisons among drugs in biologic-experienced patients

Statement 5: For adults with moderate-to-severe CD refractory to at least one biologic, IG-IBD makes no recommendation on the use of:
- **infliximab over adalimumab, vedolizumab or ustekinumab** (*No recommendation. Knowledge gap. Agreement rate: 84%*)
- **adalimumab over vedolizumab or ustekinumab, and**
- **vedolizumab over ustekinumab.**

(*No recommendation. Very low-quality evidence. Agreement rate: 84%*)

To induce remission in adults with moderate-to-severe CD refractory to at least one biologic, IG-IBD is unable to recommend a preferred drug between infliximab and the other three biologics (PICO 06, PICO 47, and PICO 48, respectively). This inability is due to the lack of data on infliximab in this setting.

Only indirect comparisons are available to support the choice between adalimumab and vedolizumab or between adalimumab and ustekinumab, for patients with moderate-to-severe CD who were already found to be refractory to biological therapy (PICO 49 and PICO 50, respectively). Because of indirectness, together with imprecision in clinical remission and SAEs, the evidence was considered of very low quality (PICOs 49 and 50). Regarding the comparison between adalimumab and vedolizumab, there were no differences in clinical remission (RR, 2.40; 95% CI, 0.96–6.03) and clinical response (RR, 1.02; 95% CI, 0.64–1.63). Evidence was also sought for mucosal healing, but data were insufficient. Notably, a lower risk of SAEs was reported for adalimumab (RR, 0.57; 95% CI, 0.34–0.94). Similarly, for the comparison between adalimumab and ustekinumab, there were no differences between the two drugs regarding clinical remission (RR, 1.31; 95% CI, 0.61–2.84) and clinical response (RR, 0.87; 95% CI, 0.62–1.23), while data on mucosal healing were insufficient. Furthermore, no difference was observed regarding the safety outcomes of AEs (RR, 1.01; 95% CI, 0.89–1.15) and SAEs (RR, 0.75; 95% CI, 0.45–1.25).

The overall quality of evidence for the comparison between vedolizumab and ustekinumab in biologic-experienced patients was very low (because of indirectness, together with imprecision in clinical remission and SAEs) (PICO 15). There were no differences between the two drugs regarding the efficacy outcomes of clinical remission (RR, 0.55; 95% CI, 0.23–1.29) and clinical response (RR, 0.85; 95% CI, 0.53–1.36), while data on mucosal healing were insufficient. Furthermore, no difference was observed regarding the safety outcomes of AEs (RR, 1.05; 95% CI, 0.96–1.16) and SAEs (RR, 1.32; 95% CI, 0.82–2.11).

Panel comment beyond GRADE: The use of vedolizumab and ustekinumab as second-line agents in CD patients has been compared in recent real-world studies. While some studies suggested that ustekinumab was associated with higher long-term effectiveness than vedolizumab [30–33], other studies did not find significant differences [34,35], or slightly favored the use of vedolizumab [36].

4. Setting 2: anti-TNF-based combination therapy for the induction of remission in adults with moderate-to-severe CD

Statement 6: For adults with moderate-to-severe CD refractory to conventional therapy, IG-IBD recommends using combination therapy with infliximab plus an immunosuppressant rather than infliximab monotherapy for the induction of remission. (*Strong recommendation. Moderate-quality evidence. Agreement rate: 72%*)

IG-IBD recommends using combination therapy with infliximab plus an immunosuppressant (thiopurines or methotrexate), instead of infliximab monotherapy, in adults with moderate-to-severe CD refractory to conventional therapy (PICO 16). The overall quality of evidence was moderate due to serious imprecision (sparse data) for mucosal healing and SAEs. A slight but significant superiority of combination therapy was detected for all critical outcomes, including clinical remission (RR, 1.29; 95% CI, 1.01–1.64), clinical response (RR, 1.24; 95% CI, 1.05–1.47), and mucosal healing (RR, 1.46; 95% CI 1.00–2.13). A lower risk of SAEs was reported for the combination therapy (RR, 0.62; 95% CI, 0.40–0.96).

Panel comment beyond GRADE: This recommendation arises from two studies that assessed clinical remission at 10–12 weeks, clinical response at 10 weeks, and mucosal healing at 26 weeks. Therefore, evidence for a clinical benefit exists, as also highlighted by a prospective study [37], but it is actually limited to short-term outcomes.

Statement 7: For adults with moderate-to-severe CD refractory to conventional therapy, IG-IBD makes no recommendation in the choice between combination therapy with adalimumab plus an immunosuppressant and adalimumab monotherapy for the induction of remission. (*No recommendation. Very low-quality evidence. Agreement rate: 84%*)

IG-IBD makes no recommendation regarding the choice between combination therapy with adalimumab plus an immunosuppressant and adalimumab monotherapy for inducing remission of CD (PICO 17). The overall quality of evidence was very low, because the evidence came from two studies at serious risk of bias and there was serious imprecision due to sparse data. Combination therapy with adalimumab plus an immunosuppressant was superior to adalimumab monotherapy for the achievement of mucosal healing (RR, 1.32; 95% CI, 1.06–1.65). However, there was serious indirectness for this outcome, as the evidence for healing was inferred from endoscopic improvement, defined as a decrease of SES-CD of at least 8 points from baseline or SES-CD $\leq$ 4. Furthermore, no difference was detected for the two different strategies regarding the other efficacy and safety outcomes. The RRs for clinical remission and clinical response were 0.95 (95% CI, 0.78–1.15) and 0.93 (95% CI, 0.79–1.11), respectively, while the RR of SAEs was 1.23 (95% CI, 0.80–1.89).

Panel comment beyond GRADE: It should be noted that, according to a recent cohort study (PANTS) of anti-TNF agent-naive patients [37], combination immunomodulator therapy reduced the risk of developing antibodies against both infliximab and adalimumab, therefore influencing one-year remission rates.

5. Setting 3: maintenance of remission induced by biologics

Statement 8: For adults with CD who achieve remission with infliximab, adalimumab, vedolizumab or ustekinumab, IG-IBD recommends using the same drug as maintenance treatment. *(Strong recommendation. Very low-quality evidence for infliximab, low-quality evidence for adalimumab and ustekinumab, and high-quality evidence for vedolizumab. Agreement rate: 100%)*

Although the quality of evidence was not the same for every biologic, IG-IBD panel decided to recommend as maintenance treatment the same drug through which remission was achieved at induction. Regarding infliximab (PICO 18), the overall quality of evidence was very low, mainly because of the serious risk of bias regarding mucosal healing (incomplete accounting of patients and outcome events) and the very serious imprecision (sparse data and wide CI). The statement is based on one study for efficacy outcomes and three studies for safety, showing that infliximab was superior to placebo for maintaining clinical remission (RR, 2.08; 95% CI, 1.19–3.61) but not mucosal healing (RR, 6.36; 95% CI, 0.86–46.9). Infliximab and placebo posed similar risks of AEs (RR, 1.01; 95% CI, 0.94–1.08) and SAEs (RR, 0.77; 95% CI, 0.51–1.17).

Similarly, Ig-IBD recommends using adalimumab as maintenance treatment in adults with CD who achieved remission with this drug, even if the quality of evidence was judged to be low due to inconsistency on AEs (heterogeneity) and to imprecision on mucosal healing (sparse data and very wide CI; PICO 19). The statement is based on four studies for clinical remission, one for mucosal healing, and eight for AEs and SAEs. Adalimumab was superior to placebo in maintaining clinical remission (RR, 2.68; 95% CI, 1.88–3.83) and mucosal healing (RR, 31.23; 95% CI, 1.93–505.7). Furthermore, adalimumab and placebo posed similar risks of AEs (RR, 0.97; 95% CI, 0.87–1.08). Conversely, treatment with adalimumab was associated with a lower risk of SAEs (RR, 0.59; 95% CI, 0.40–0.86).

Regarding vedolizumab, there was enough evidence to recommend it as maintenance treatment in adults with CD that went into remission with this drug (PICO 20). The statement is based on two studies that clearly showed that vedolizumab was superior to placebo in maintaining clinical remission (RR, 1.84; 95% CI, 1.30–2.61). Data were insufficient for drawing conclusions on mucosal healing. In the five studies reporting safety data, vedolizumab and placebo had similar risks of AEs (RR, 1.01; 95% CI, 0.95–1.09) and SAEs (RR, 1.04; 95% CI, 0.75–1.44).

Finally, IG-IBD recommends using ustekinumab as maintenance treatment in adults with CD who underwent remission with this drug. The quality of evidence was low due to very serious imprecision (sparse data and very wide CI) for mucosal healing (PICO 21). The statement is based on two studies for clinical remission, one study for mucosal healing, and five studies for safety outcomes. Ustekinumab was superior to placebo in maintaining clinical remission (RR, 1.47; 95% CI, 1.16–1.88), but no significant differences were found in terms of mucosal healing (RR, 4.14, 95% CI, 0.52–33.1). Ustekinumab and placebo had similar risks of AEs (RR, 0.96; 95% CI, 0.90–1.02) and SAEs (RR, 0.79; 95% CI, 0.56–1.11).

Panel comment beyond GRADE: Although the ideal therapeutic target is still undefined in CD, the concept of transmural healing (or remission) is emerging in the last years as a relevant endpoint, potentially associated with favorable long-term outcomes [38]. However, further studies are needed to better clarify the clinical benefit of achieving transmural healing on disease course (in terms of steroids need, hospitalization, and surgery).

6. Setting 4: optimization strategies and de-escalation of anti-TNF-based treatments

Statement 9: For adults with CD who achieve remission with an anti-TNF agent plus an immunosuppressant, IG-IBD makes no recommendation on the choice between combination therapy with infliximab or adalimumab plus an immunosuppressant and either infliximab or adalimumab monotherapy (*No recommendation. Very low-quality evidence. Agreement rate: 64%)* **or immunosuppressant monotherapy for the long-term maintenance of remission** (*No recommendation. Knowledge gap. Agreement rate: 60%).*

The panel makes no recommendation on the choice between an anti-TNF agent (infliximab, adalimumab) combined with an immunosuppressant and anti-TNF monotherapy for long-term maintenance in adults with CD who achieved remission with an anti-TNF agent plus an immunosuppressant (PICOs 28 and 29). Still, the general recommendation is to maintain the combination therapy as long as it decreases the immunogenic risk of the specific biologic, also because there are well-known safety concerns about long-term combination therapies [39,40]. Only limited evidence came from two open-label, prospective, randomized controlled trials (RCTs) that compared a combination therapy (either infliximab or adalimumab plus azathioprine) to either infliximab or adalimumab monotherapy. In both studies, no significant difference between these treatments was observed in terms of clinical remission (RR, 0.89; 95% CI, 0.53–1.48, and RR, 1.03; 95% CI, 0.90–1.18, respectively) and mucosal healing (RR, 1.14; 95% CI, 0.65–2.02, and RR, 0.95; 95% CI, 0.39–2.35, respectively). Combination therapy and anti-TNF monotherapy posed a similar risk of AEs (RR, 0.96; 95% CI, 0.68–1.36, and RR, 0.32; 95% CI, 0.04–2.65, respectively). Regarding SAEs, no differences were observed between infliximab plus azathioprine and infliximab monotherapy (RR, 1.00; 95% CI, 0.21–4.66). No SAEs were reported in the study with adalimumab. The overall quality was very low for the serious risk of bias due to study design (both open-label studies) and very serious imprecision for all outcomes explored (sparse data and wide CI).

There is insufficient comparative evidence between combination therapy with an anti-TNF agent (infliximab or adalimumab) plus an immunosuppressant and immunosuppressant monotherapy as maintenance treatment (PICOs 30 and 31).

Statement 10: For adults with CD who have lost the response to anti-TNF agents, IG-IBD makes no recommendation on using therapeutic drug monitoring or a standard symptom-based approach of dose optimization. (*No recommendation. Very low-quality evidence. Agreement rate: 72%*)

For adult CD patients who have lost the response to anti-TNF agents, IG-IBD makes no recommendation regarding the use of therapeutic drug monitoring or a standard symptom-based approach of dose optimization (PICO 32). In the RCT that compared therapeutic drug monitoring to a clinic-based approach, no differences were observed regarding clinical remission (RR, 0.78; 95% CI, 0.40–1.51) or clinical response (RR, 1.09; 95% CI, 0.71–1.67). The overall quality of evidence was very low due to serious risk of bias and very serious imprecision.

Panel comment beyond GRADE: Therapeutic drug monitoring, when available, can be used to drive therapeutic choices in case

of non-response or loss of response with anti-TNF agents, as also suggested by a recent consensus statement [41].

Statement 11: For adults with CD who have lost the response to anti-TNF agents and do not respond to dose escalation, IG-IBD makes no recommendation on using an anti-TNF agent plus an immunosuppressant or making a therapeutic change. (*No recommendation. Knowledge gap. Agreement rate: 76%)*

IG-IBD makes no recommendation on the choice between adding an immunomodulator to an anti-TNF agent and changing the therapeutic strategy when the response to an anti-TNF agent is lost. There is insufficient evidence to inform this clinical question (PICO 33).

Panel comment beyond GRADE: Given the current availability of biologics with different mechanisms of action, the option of trying a different biological drug seems to be gaining preference among clinicians. Instead, there is a reduced tendency to add an immunosuppressant to the anti-TNF agent.

Statement 12: For adults with CD who achieved long-term deep remission, IG-IBD makes no recommendation about the withdrawal of anti-TNF treatment. *(No recommendation. Knowledge gap. Agreement rate: 84%)*

The evidence is very limited to inform this clinical question (PICO 34).

Panel comment beyond GRADE: Ideally, deep remission in CD should include clinical, biochemical, endoscopic, and transmural remission [42]. The possibility of withdrawing an anti-TNF agent when long-term deep remission has been achieved should be assessed on a case-by-case basis and discussed with the patient. Factors to consider include the higher rate of continued clinical remission in patients who continue anti-TNF treatment and the risk of relapse in case of discontinuation [43,44]. Patients who relapse after discontinuation may have high chances of re-gaining remission when treatment is resumed, as recently suggested [45].

7. Setting 5: complex perianal CD

Statement 13: In adult patients with complex perianal CD, IG-IBD recommends using infliximab *(Strong recommendation. Low-quality evidence. Agreement rate: 100%)* **and suggests using adalimumab**. *(Conditional recommendation. Low-quality evidence. Agreement rate: 96%)*

In adult patients with complex perianal CD, IG-IBD recommends using infliximab. Compared to placebo or no treatment, the RR for achieving fistula healing or closure was 4.25 (95% CI, 1.61–11.20), with low-quality evidence (PICO 35). The RR for maintaining fistula healing or closure was 1.79 (95% CI, 1.10–2.92). Considering safety, the RR for AEs was 0.97 (95% CI, 0.90–1.04), and the RR for SAEs was 0.63 (95% CI, 0.38–1.04)

IG-IBD suggests using adalimumab for adults with complex perianal CD (PICO 36). While no difference was observed between adalimumab and placebo (or no treatment) in achieving fistula healing or closure (RR, 0.43; 95% CI, 0.07–2.55), the biologic was superior to placebo in maintaining fistula healing or closure (RR, 2.87; 95% CI, 1.19–6.95). However, the overall quality of evidence was low, and when evidence was sought for safety outcomes (AEs and SAEs), data were insufficient to draw any conclusion.

Statement 14: In adult patients with complex perianal CD, IG-IBD suggests using infliximab over adalimumab. *(Conditional recommendation. Very low-quality evidence. Agreement rate: 88%)*

IG-IBD suggests using infliximab over adalimumab in adults with complex perianal CD. The recommendation is conditional due to very low-quality evidence (PICO 37). Based on an indirect comparison, infliximab was superior to adalimumab for the short-term critical outcome of fistula healing/closure (RR, 9.88; 95% CI, 1.28–76.2). In contrast, there was no difference between the drugs for the long-term critical outcome of maintaining fistula healing or closure (RR, 0.62; 95% CI, 0.23–1.71). Data were insufficient to assess comparative safety (overall AEs and SAEs).

Statement 15: In adult patients with complex perianal CD, IG-IBD makes no recommendation for using vedolizumab or ustekinumab. *(No recommendation. Very low-quality evidence for vedolizumab and low-quality evidence for ustekinumab. Agreement rate: 100%)*

IG-IBD makes no recommendation for using vedolizumab or ustekinumab in adult patients with complex perianal CD (PICO 38 and 39, respectively). The potential efficacy of vedolizumab for complex perianal CD was examined in only one post-hoc exploratory subgroup analysis of the GEMINI 2 trial, and no significant difference was observed between the vedolizumab and placebo arms in the rate of fistula healing or closure (RR, 2.23; 95% CI, 0.57–8.72). Regarding ustekinumab, a pooled analysis of patients enrolled in the UNITI-1, UNITI-2 and CERTIFI studies revealed no difference compared to placebo in terms of achieving fistula healing or closure (RR, 1.98; 95% CI, 0.98–4.00). Finally, evidence was also sought for AEs and SAEs, but data were insufficient for both vedolizumab and ustekinumab.

Panel comment beyond GRADE: The outcomes of perianal disease have rarely been evaluated objectively, so the evidence has poor reliability. Therefore, it is not easy to precisely evaluate the efficacy of the different treatments, and this could explain the unmet needs persisting in the setting of perianal disease [46].

Statement 16: In adult patients with complex perianal CD that showed an inadequate response to one or more biologic therapy, IG-IBD suggests using darvadstrocel. *(Conditional recommendation. Low-quality evidence. Agreement rate: 92%)*

In adults with complex perianal CD refractory to biological treatment, the panel suggests using darvadstrocel, a therapy consisting of allogenic expanded adipose-derived mesenchymal stromal cells (PICO 40). This therapy was approved based on a single RCT (ADMIRE-CD), which found a nonsignificant difference in favor of darvadstrocel over placebo in achieving fistula healing or closure at week 24 (RR, 1.30; 95% CI, 0.97–1.74) and a significant difference for the same outcome at week 52 (RR, 1.43; 95% CI, 1.07–1.90). Regarding safety, no statistically significant differences were observed

Table 3
Use of biologics for moderate-to-severe Crohn's disease: practice guidelines and evidence.

Statement	Quality of evidence	Agreement rate	Panel comment beyond GRADE
1. For adults with moderate-to-severe CD refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, vedolizumab or ustekinumab to induce remission.	Moderate for infliximab, adalimumab and vedolizumab. Very low for ustekinumab	100%	Biosimilars of infliximab and adalimumab have equivalent efficacy and safety to the originator products and cost less than the originator products Their availability reinforces our recommendation to use these two drugs as first-line biologics in most patients. We expect to be able to make a similar recommendation for vedolizumab and ustekinumab when low-cost biosimilars for these two drugs become available. Most studies investigated vedolizumab and ustekinumab as second-line agents. Nonetheless, recent studies demonstrated the effectiveness of these drugs in patients who were naïve to biologics.
2. For adults with moderate-to-severe active CD, refractory to conventional therapy, who are naïve to biologics, IG-IBD makes no recommendation on the preferential use of: - infliximab over adalimumab, vedolizumab, or ustekinumab - adalimumab over vedolizumab or ustekinumab, or - vedolizumab over ustekinumab.	Very low for all comparisons, except for moderate quality for adalimumab vs. ustekinumab	88%	Several large, real-world studies have highlighted the substantial equality in effectiveness between infliximab and adalimumab for CD patients who are naïve to biologics. Real-world evidence has demonstrated a similar effectiveness between adalimumab and vedolizumab in CD patients, both naïve and experienced to biologics.
3. For adults with moderate-to-severe CD refractory to a previous therapy with adalimumab, IG-IBD makes no recommendation in favor of or against using infliximab to induce remission.	Knowledge gap	64%	Twenty years of clinical experience with infliximab and demonstrated efficacy in observational studies suggest that it may also be effective in patients in whom previous treatment with adalimumab was unsuccessful. However, it should be noted that the current availability of several biologics with different mechanisms of action is reducing clinicians' tendency to switch from one anti-TNF agent to another, particularly in cases of primary nonresponse. Conversely, a switch from one anti-TNF agent to another should be considered when an effective anti-TNF agent must be withdrawn due to intolerance.
4. For adults with moderate-to-severe CD refractory to at least one biologic, IG-IBD recommends using adalimumab, vedolizumab or ustekinumab to induce remission.	Moderate for adalimumab and vedolizumab. Very low for ustekinumab	80%	Vedolizumab has been shown to be effective and safe in patients with CD, and it has frequently been administered as a second-line biologic in clinical practice. Consequently, despite the drug being superior to placebo only for clinical response (a critical outcome), IG-IBD decided to give a strong recommendation for vedolizumab. Similarly to vedolizumab, ustekinumab has been used in clinical practice mostly in patients who were previously exposed to another biologic. The drug demonstrated clear effectiveness in this setting.
5. For adults with moderate-to-severe CD refractory to at least one biologic, IG-IBD makes no recommendation on the use of: - infliximab over adalimumab, vedolizumab or ustekinumab - adalimumab over vedolizumab or ustekinumab, and - vedolizumab over ustekinumab.	Knowledge gap for the comparisons involving infliximab. Very-low for all other comparisons	84%	The use of vedolizumab and ustekinumab as second-line agents in CD patients has been compared in recent real-world studies. While four studies suggested that ustekinumab is associated with higher long-term effectiveness than vedolizumab, other studies did not find significant differences or slightly favored the use of vedolizumab.
6. For adults with moderate-to-severe CD refractory to conventional therapy, IG-IBD recommends using combination therapy with infliximab plus an immunosuppressant rather than infliximab monotherapy for the induction of remission.	Moderate	72%	This recommendation arises from two studies that assessed clinical remission at 10–12 weeks, clinical response at 10 weeks, and mucosal healing at 26 weeks. Therefore, evidence for a clinical benefit exists, but it is probably limited to short-term outcomes.
7. For adults with moderate-to-severe CD refractory to conventional therapy, IG-IBD makes no recommendation in the choice between combination therapy with adalimumab plus an immunosuppressant and adalimumab monotherapy for the induction of remission.	Very low	84%	It should be noted that, according to a recent cohort study (PANTS) of anti-TNF agent-naive patients, combination immunomodulator therapy reduced the risk of developing antibodies against both infliximab and adalimumab, therefore influencing one-year remission rates.

(*continued on next page*)

Table 3 (*continued*)

Statement	Quality of evidence	Agreement rate	Panel comment beyond GRADE
8. For adults with CD who achieve remission with infliximab, adalimumab, vedolizumab or ustekinumab, IG-IBD recommends using the same drug as maintenance treatment.	Very low for infliximab. Low for adalimumab and ustekinumab. High for vedolizumab	100%	Although the ideal long-term therapeutic target is still undefined in CD, the concept of transmural healing (or remission) is emerging in the last years as a relevant outcome associated with favorable long-term outcomes.
9. For adults with CD who achieve remission with an anti-TNF agent plus an immunosuppressant, IG-IBD makes no recommendation on the choice between combination therapy with infliximab or adalimumab plus an immunosuppressant and either infliximab or adalimumab monotherapy *or* immunosuppressant monotherapy for the long-term maintenance of remission.	Very low (first part). Knowledge gap (second part)	64% (first part). 60% (second part)	
10. For adults with CD who have lost the response to anti-TNF agents, IG-IBD makes no recommendation on using therapeutic drug monitoring or a standard symptom-based approach of dose optimization.	Very low	72%	Therapeutic drug monitoring, when available, can be used to drive therapeutic choices in case of non-response or loss of response with anti-TNF agents.
11. For adults with CD who have lost the response to anti-TNF agents and do not respond to dose escalation, IG-IBD makes no recommendation on using an anti-TNF agent plus an immunosuppressant or making a therapeutic change.	Knowledge gap	76%	No studies have been done specifically in this setting. However, given the availability of biologics with different mechanisms of action, the option of trying a different biological drug seems to be gaining preference among clinicians. Instead, there is a reduced tendency to add an immunosuppressant to the anti-TNF agent.
12. For adults with CD who achieved long-term deep remission, IG-IBD makes no recommendation about the withdrawal of anti-TNF treatment.	Knowledge gap	84%	Ideally, deep remission in CD should include clinical, biochemical, endoscopic, and transmural remission. The possibility of withdrawing an anti-TNF agent when long-term deep remission has been achieved should be assessed on a case-by-case basis and discussed with the patient. Factors to consider include the higher rate of continued clinical remission in patients who continue anti-TNF treatment and the risk of relapse in case of discontinuation. Patients who relapse after discontinuation may have high chances of re-gaining remission when treatment is resumed.
13. **I**n adult patients with complex perianal CD, IG-IBD recommends using infliximab and suggests using adalimumab.	Low	100% for infliximab. 96% for adalimumab	
14. In adult patients with complex perianal CD, IG-IBD suggests using infliximab over adalimumab.	Very low	88%	
15. In adult patients with complex perianal CD, IG-IBD makes no recommendation for using vedolizumab or ustekinumab.	Very low for vedolizumab. Low for ustekinumab	100%	The outcomes of perianal disease have rarely been evaluated objectively, so the evidence has poor reliability. Therefore, it is not easy to precisely evaluate the efficacy of the different treatments, and this could explain the unmet needs persisting in the setting of perianal disease.
16. In adult patients with complex perianal CD that showed an inadequate response to one or more biologic therapy, IG-IBD suggests using darvadstrocel.	Low	92%	This advanced therapy is still rarely used in clinical practice. Its administration requires a surgeon trained in the procedure working in a tertiary referral center.
17. In adults with CD at high risk for post-operative recurrence, IG-IBD recommends using infliximab and suggests using adalimumab.	Moderate for infliximab. Very low for adalimumab	96%	
18. In adults with CD at high risk for post-operative recurrence, IG-IBD makes no recommendation for using infliximab over adalimumab.	Very low	100%	
19. In adults with CD at high risk for post-operative recurrence, IG-IBD makes no recommendation for using vedolizumab or ustekinumab.	Knowledge gap	80%	Almost all studies on the prevention of the post-operative recurrence of CD focused on anti-TNF agents. Regarding the new biologics, one study investigated the effectiveness of vedolizumab against the recurrence – but not for the prevention - of post-operative CD, showing potential benefit of the drug.

between darvadstrocel and placebo in terms of AEs (RR, 1.06; 95% CI, 0.90–1.24) and SAEs (RR, 1.18; 95% CI, 0.71–1.97).

Panel comment beyond GRADE: This advanced therapy is still rarely used in clinical practice. Its administration requires a surgeon trained in the procedure working in a tertiary referral center.

8. Setting 6: prevention of post-operative recurrence of CD

Statement 17: In adults with CD at high risk for post-operative recurrence, IG-IBD recommends using infliximab *(Strong recommendation. Moderate-quality evidence. Agreement rate: 96%)* **and suggests using adalimumab.** *(Conditional recommendation. Very low-quality evidence. Agreement rate: 96%)*

The panel recommends using infliximab in adults with CD at high risk for post-operative recurrence (PICO 41). The evidence for infliximab came from four RCTs that showed clear superiority over placebo for maintaining endoscopic remission (RR, 3.44; 95% CI, 1.36–8.71) but not for maintaining clinical remission (RR, 1.24; 95% CI, 0.90–1.71). Regarding safety outcomes, no significant difference was observed between infliximab and placebo in terms of AEs (RR, 1.15; 95% CI, 0.72–1.84) and SAEs (RR, 0.87; 95% CI, 0.56–1.35). The overall quality of evidence was moderate.

IG-IBD suggests using adalimumab in adults with CD at high risk for post-operative recurrence (PICO 42). Evidence for the efficacy of adalimumab came from indirect treatment comparisons showing its superiority over placebo or no treatment for maintaining endoscopic remission (RR, 3.87; 95% CI, 1.42–10.5) but not for maintaining clinical remission (RR, 1.24; 95% CI, 0.80–1.91). The overall quality of evidence was rated as very low. Data were insufficient for evaluating comparative safety outcomes (AEs and SAEs).

Statement 18: In adults with CD at high risk for post-operative recurrence, IG-IBD makes no recommendation for using infliximab over adalimumab. *(No recommendation. Very low-quality evidence. Agreement rate: 100%)*

IG-IBD makes no recommendation for using infliximab over adalimumab in adults with CD at high risk for post-operative recurrence (PICO 43). No RCT on this topic has been reported. One small, open-label study found no difference in efficacy between the two biologics.

Statement 19: In adults with CD at high risk for post-operative recurrence, IG-IBD makes no recommendation for using vedolizumab or ustekinumab. *(No recommendation. Knowledge gap. Agreement rate: 80%)*

IG-IBD makes no recommendation for using vedolizumab or ustekinumab in the management of the post-operative recurrence of CD (PICO 44 and 45). In fact, evidence is too limited to inform these clinical questions.

Panel comment beyond GRADE: Almost all studies on the prevention of the post-operative recurrence of CD focused on anti-TNF agents. Regarding the new biologics, one study investigated the effectiveness of vedolizumab against the recurrence – but not for the prevention - of post-operative CD, showing potential benefit of the drug [47]. There are no data on ustekinumab.

9. Conclusion

These 19 statements are intended as a guide for clinicians caring for patients with moderate-to-severe CD (Table 3). Unfortunately, it was not possible to formulate a recommendation for several topics. This was due not to a weakness of the GRADE methodology, but to the lack of adequate data from RCTs. Lack of evidence is responsible for the current remarkable difficulty in comprehensively positioning biologics in CD. Consequently, pending new trials and head-to-head comparisons between drugs, reports of real-world experience are needed to boost the overall evidence. Furthermore, although SAEs rate was considered a critical outcome, we acknowledge that RCTs – the basis of these guidelines - are not the best tool to assess safety, while differences in serious infection rates existing between different biologics [48] were not taken into account as a separate outcome. Therefore, we believe that our inclusion of comments based on the real-world experiences will help overcome, at least in part, the scarcity of robust research studies.

Declaration of Competing Interest

FSM served as an advisory board member and/or received lecture grants from AbbVie, Biogen, Galapagos, Janssen, MSD, Pfizer, Samsung Bioepis, and Takeda Pharmaceuticals. CP has received consultancy fees and/or educational grants from Abbvie, MSD, Takeda, Pfizer, Janssen-Cilag, Sandoz, Chiesi, Sofar, Ferring and Zambon. SF: advisory board for Janssen Cilag; consultancy fees and/or educational grants from Takeda, SoFar, Abbvie, Zambon. AO served as an advisory board member for AbbVie, Galapagos, MSD, Janssen, Pfizer, Takeda Pharmaceuticals, and received lecture grants from AbbVie, MSD, Sofar, Chiesi, Janssen, Pfizer, and Takeda Pharmaceuticals. DP received consultancy fees from Takeda, Jannsen-Cilag, Pfizer, and MSD. GF served as a consultant and advisory board member for Takeda, Abbvie, Janssen, Pfizer, Celltrion, Sandoz, AlfaSigma, Samsung Bioepis, Amgen, Roche, Ferring, Mylan, Galapagos. MCF received consultancy fees from Roche, Takeda, Jannsen-Cilag, Pfizer, Sandoz, Biogen, Galapagos and research economic support from Abbvie. FC served as consultant to Abbvie, MSD, Takeda, Janssen, Roche, Celgene, Bristol-Meyers Squipp, Galapagos, Gllead, Pfizer, Mundipharma, Galapagos, Biogen, received lecture fees from Abbvie, Ferring, Takeda, Allergy Therapeutics, Janssen, Pfizer, Biogen, and unrestricted research grants from Giuliani, Sofar, MSD, Takeda, Abbvie. MD served as advisor or received consultancy fees from: Roche, Takeda, Janssen, Pfizer, Abbvie, Bioclinica. AA: consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Arena, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mylan, Pfizer, Protegonist-Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mitsubishi Tanabe, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Tigenix; research grants: MSD, Pfizer, Takeda, and Biogen. SB, CP, and DP have no conflicts of interest to declare.

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