Guidelines

Use of biologics and small molecule drugs for the management of moderate to severe ulcerative colitis: IG-IBD clinical guidelines based on the GRADE methodology ☆

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ABSTRACT

The management of moderate to severe ulcerative colitis has undergone significant changes over the past 15 years due to the regulatory approval of several new drugs. In particular, following the approval of the first biological, i.e. infliximab, a number of further biological drugs, such as adalimumab, golimumab, vedolizumab and ustekinumab, and small molecules, such as tofacitinib, have been approved, thus enriching the therapeutic armamentarium for ulcerative colitis. Choice of therapy must take into consideration not only the need to induce and maintain disease remission according to the patient's profile, but also age, co-morbidities, and prior treatments. To guide these decisions, the Italian Group for the Study of Inflammatory Bowel Disease has developed clinical guidelines that supersede its earlier document from 2011. These new guidelines were developed following the GRADE methodology for rating the quality of the evidence and for determining the strength of the recommendations. This article presents the methodology and results, in the form of 20 statements with commentary on the use of the five biologics and tofacitinib for managing the intestinal manifestations of active ulcerative colitis and for maintaining remission. A separate technical review reports the analyses of the evidence upon which the present recommendations are based.

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition whose natural history is characterized by relapsing and remitting inflammation [1]. Although most patients have a mild or moderate course, for approximately 15–20% of cases the disease behavior is more aggressive. In addition, 20% of patients with moderate or se-

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vere UC require hospitalization, and the 5- and 10-year cumulative risks of colectomy are not negligible, being about 10% and 15%, respectively [2]. As a result, biological therapy has been an important step forward in the treatment of patients with moderate to severe UC. For several years, the most advanced therapies for these patients were based on blocking the activity of tumor necrosis factor (TNF), a pharmacological mechanism of action that has proven to be effective in improving all clinical outcomes [3]. Infliximab was the first biologic approved for the treatment of UC, and it was followed by two additional anti-TNF agents, namely adalimumab and golimumab. More recently, the introduction of vedolizumab expanded the therapeutic armamentarium for UC thanks to its novel mechanism of action – the gut-selective inhibition of $\alpha_4\beta_7$ integrin [4]. Ustekinumab – an inhibitor of subunit p40 of interleukin 12 and 23 that was already used for Crohn's disease [5,6] – is the most recently approved biologic for the treatment of UC. Finally, the small molecule drug tofacitinib is the first of its class (i.e. orally administered inhibitors of janus kinases) to be approved for the treatment of moderate to severe UC [7].

The American Gastroenterological Association [8] and the European Crohn's and Colitis Organization [9] have both recently published clinical practice guidelines on the management of UC. However, both guidelines took a broad view not limited to the use of biologics or small molecule drugs for UC, which is the focus of the present guidelines. Furthermore, national recommendations are necessary to guide physicians dealing with inflammatory bowel disease (IBD) in different countries because of the different economic and legal issues that may impact on the possibility to prescribe drugs. In Italy, guidelines on the use of anti-TNF agents in IBD were published in 2011 by the Italian Society of Gastroenterology and the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) [10]. Ten years later, these guidelines are considered outdated given the recent expansion in treatment options for these diseases. In addition, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach has emerged as the reference method for developing high-quality, evidence-based recommendations for clinical practice [11]. The GRADE approach was used for the development of these new guidelines, not only for synthesizing the evidence, but also for making evidence-based comparisons of the efficacies of different UC drugs and for drawing indications about therapeutic decision making.

Given the premises, this document presents the official recommendations of IG-IBD on the use of biologics and small molecule drugs for the management of moderate to severe UC. Notably, the guidelines focus on intestinal outcomes and do not provide indications for treating extra-intestinal manifestations, refractory pouchitis, or the management of biological therapy during pregnancy. The guidelines were developed using the GRADE approach and are accompanied by a technical review [12] 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 guidelines development

The steps for guidelines development are depicted in Fig. 1. A first meeting was held in March 2019, so the entire process (which also involved the development of guidelines for Crohn's disease) took approximately 2 years. Although tofacitinib and ustekinumab were not entered in clinical practice on that date, it was decided to include them in the guidelines as they were expected to be available in the near future for the treatment of UC. The following work groups were created to involve, with different tasks, as many Italian IBD experts as possible: (i) *steering committee* (6 IG-IBD mem-

bers), which coordinated and promoted the project; (ii) *working panel* (25 IG-IBD members and 2 representatives of patients' associations), which was involved in the various rounds of voting and in revising the statements; (iii) *methodology panel* (3 non-IG-IBD members), which did the systematic literature search, summarized the evidence according to the GRADE approach, and drafted the technical review; and (iv) *review panel* (19 IG-IBD members), who offered expert opinions on late drafts of the manuscript.

The first step of the process was to formulate the clinical questions and related outcomes of interest. This task was done by the steering committee, which identified five main clinical settings:

– *Setting 1*: Induction of remission in adults with moderate to severe UC. This setting was divided into four sub-settings:
  – 1A: Biologics or tofacitinib vs. no treatment in biologic-naïve patients
  – 1B: Comparisons among drugs in biologic-naïve patients
  – 1C: Biologics or tofacitinib 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 UC
– *Setting 3*: Acute severe UC refractory to intravenous steroids
– *Setting 4*: Maintenance of remission induced by biologics or tofacitinib
– *Setting 5*: Optimization strategies and de-escalation of anti-TNF-based treatments.

Subsequently, the methodology panel translated each clinical question into PICO elements (patient population, intervention, comparator, outcome of interest). Seventy-five PICOs were formulated, and a systematic literature search was performed (see the technical review [12] for details). Meanwhile, a web-based round of voting was conducted so that the working panel could define the importance of the outcomes (i.e. critical, important but not critical, of limited importance) for each clinical setting. Then, the methodology panel started a systematic review of the literature with the consequent creation of a summary of findings table for each PICO. At the end of this process, the steering committee formulated a first round of statements, which were reviewed by 11 of the 25 IG-IBD members of the working panel (the remaining 14 were involved in developing guidelines for Crohn's disease). The final version of each statement was voted on by the whole working panel with two response options: agree or disagree. The percentage agreement is presented for each statement. A low agreement rate did not prevent formulating the recommendation, and the rate represents an additional tool for the reader to properly evaluate the validity/strength of the statements. The manuscript was drafted by the steering committee and finally revised by the review panel.

2.2. Grading of the evidence and strength of recommendations

The quality of the evidence and strength of the recommendations were evaluated according to the GRADE approach [11]. In particular, the quality of evidence was assessed by the methodology panel and indicated in the summary of findings tables. For each 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 the analytical evaluation of the overall quality of evidence for each one of the clinical questions are provided in the technical review [12].

The strength of each recommendation was defined as strong ("IG-IBD recommends...") or conditional ("IG-IBD suggests..."). The proper interpretations of the different strengths of recommendations for patients and clinicians are provided in Table 2. In line with the GRADE approach, the strength of recommendations arose

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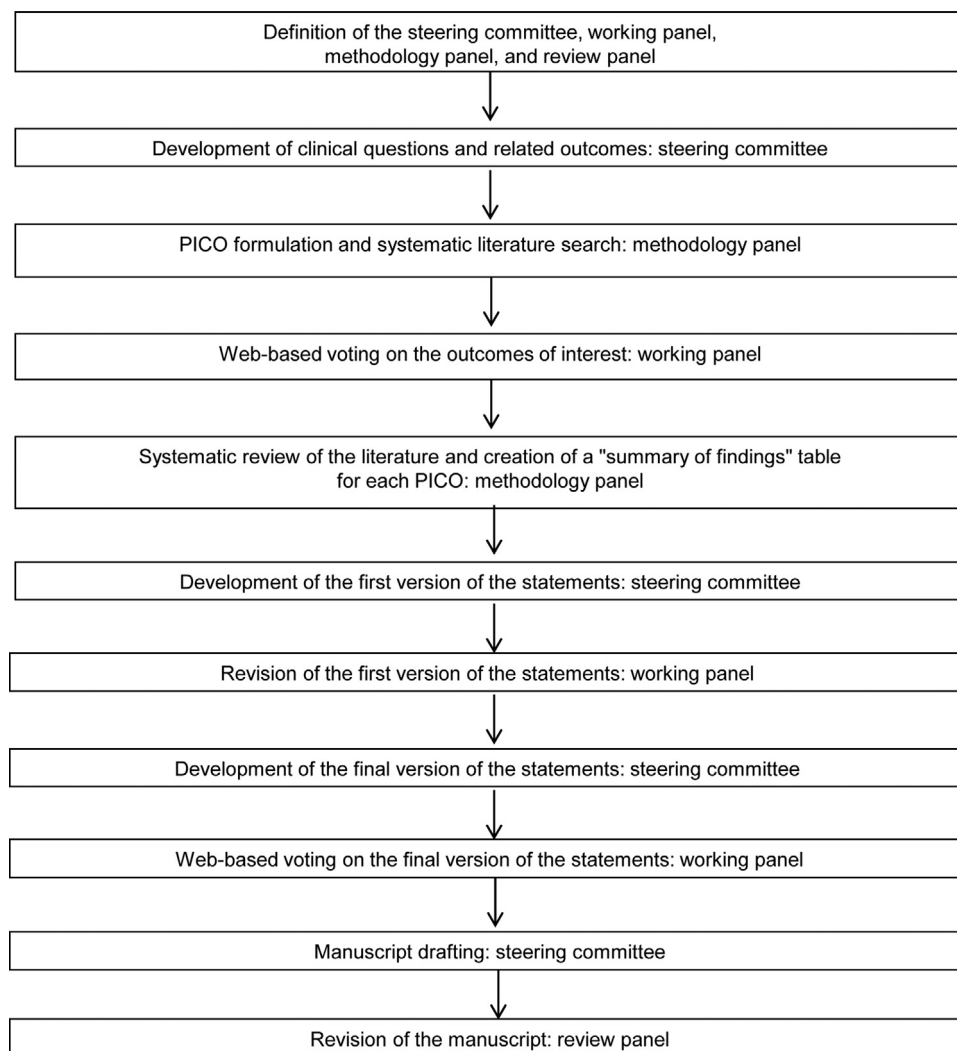
Fig. 1. Guidelines development process.

Table 1

GRADE definitions of the quality of the evidence. Modified from [11].

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 [11].

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.

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from four components: risk–benefit balance, patients' values and preferences, costs and resource allocation, and quality of evidence. Therefore, although quality of evidence was a key factor in determining the strength of the recommendations, a statement could have been classified as strong despite low-quality evidence or as conditional despite high-quality evidence when all four components were considered in its formulation [13]. The recommendations were accompanied, when necessary, by expert comments from the panel. No recommendation was made ("IG-IBD makes no recommendation…") in two cases: (a) when the confidence in the effect estimates was so low that the guideline panel felt that a recommendation would be too speculative, or when the balance between desirable and undesirable outcomes was very close, and the values and preferences were not known or variable; (b) in situations where there was no evidence to make a recommendation (i.e. knowledge gap).

2.3. Setting 1: induction of remission in adults with moderate to severe UC

2.3.1. 1A: biologics or tofacitinib vs. no treatment in biologic-naïve patients

> **Statement 1: For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib over no treatment to induce remission.** (*Strong recommendation; high-quality evidence for infliximab and adalimumab; moderate-quality evidence for vedolizumab and tofacitinib; low-quality evidence for golimumab and ustekinumab – Agreement rate: 100%*)

To induce remission of moderate to severe UC that is refractory to conventional therapy in adults who are naïve to biologics, IG-IBD recommends using any of the biologics currently available or tofacitinib. Use of these drugs is preferable to no treatment. The drugs are all effective in this setting, even if the quality of evidence is not the same for all drugs.

Regarding infliximab, the recommendation is based on five studies (see PICO 01 of the technical review [12]) that clearly showed that the drug was superior to placebo for all efficacy outcomes, including induction of clinical remission (risk ratio [RR], 2.72; 95% CI, 1.90–3.88), clinical response (RR, 1.90; 95% CI, 1.64–2.20), and mucosal healing (RR, 1.88; 95% CI, 1.59–2.23). Regarding safety outcomes, there was a slightly higher risk of adverse events (AEs) with infliximab (RR, 1.06; 95% CI, 1.01–1.12), but the risks of serious adverse events (SAEs) were similar (RR, 0.82; 95% CI, 0.61–1.10).

Similar findings were reported for adalimumab (PICO 02). Based on data from four studies that assessed efficacy at 8 weeks and three that evaluated safety at 8–52 weeks, adalimumab was superior to placebo for all efficacy outcomes, including induction of clinical remission (RR, 1.74; 95% CI, 1.17–2.59), clinical response (RR, 1.37; 95% CI, 1.19–1.58), and mucosal healing (RR, 1.33; 95% CI, 1.13–1.56). There were no differences in the risk of AEs (RR, 1.05; 95% CI, 0.94–1.19) or SAEs (RR, 0.85; 95% CI, 0.59–1.21).

Panel comment beyond GRADE: The availability of low-cost biosimilars of infliximab and adalimumab – with proven, equivalent efficacy and safety to the originator products [14–16] – reinforces the strength of the recommendation for these two biologics.

The recommendation to use golimumab for the induction of remission in adults naïve to biologics is based on three studies (PICO 03). In these studies, golimumab was superior to placebo for all efficacy outcomes (clinical remission: RR, 2.46; 95% CI, 1.56–3.89;

clinical response: RR, 1.50; 95% CI, 1.17–1.92; mucosal healing: RR, 1.42; 95% CI, 1.15–1.75), and there were similar risks of AEs (RR, 1.13; 95% CI, 0.95–1.35) and SAEs (RR, 0.71; 95% CI, 0.21–2.43). However, the overall quality of the evidence is low due to inconsistency (high heterogeneity in the data on safety) and imprecision (in the data of clinical remission and SAEs).

Evidence for the efficacy of vedolizumab for inducing remission in patients naïve to biologics comes from two studies that assessed clinical outcomes at 6–10 weeks, while safety data come from six studies with endpoints at 6–68 weeks (PICO 13). Vedolizumab was clearly superior to placebo for all efficacy outcomes, including induction of clinical remission (RR, 2.51; 95% CI, 1.37–4.60), clinical response (RR, 1.74; 95% CI, 1.26–2.40), and mucosal healing (RR, 1.77; 95% CI, 1.28–2.45). There were similar risks of AEs (RR, 1.01; 95% CI, 0.92–1.11) and SAEs (RR, 0.71; 95% CI, 0.39–1.30). Quality of evidence is moderate due to serious imprecision (sparse data).

Evidence on the efficacy of ustekinumab for inducing remission in biologic-naïve patients is based on two studies that assessed efficacy at 8 weeks and safety at 8–44 weeks. Very serious imprecision due to sparse data for clinical remission was reported; thus, the overall quality of evidence is low (PICO 60). The data, however, showed that ustekinumab was superior to placebo for all efficacy outcomes, including clinical remission (RR, 1.85; 95% CI, 1.03–3.33), clinical response (RR, 1.86; 95% CI, 1.46–2.38), and mucosal healing (RR, 1.57; 95% CI, 1.07–2.31). There were similar risks of AEs (RR, 1.00; 95% CI, 0.92–1.10) and SAEs (RR, 0.67; 95% CI, 0.39–1.17).

Regarding tofacitinib, the recommendation is based on three studies (PICO 15) for clinical remission and clinical response, two for mucosal healing, and four for AEs and SAEs. Quality of evidence is moderate due to serious imprecision (sparse data) for SAEs. Nonetheless, tofacitinib was superior to placebo for all efficacy outcomes, including induction of clinical remission (RR, 2.06; 95% CI, 1.30–3.28), clinical response (RR, 1.51; 95% CI, 1.21–1.87), and mucosal healing (RR, 1.64; 95% CI, 1.13–2.37). There were similar risks of AEs (RR, 0.99; 95% CI, 0.92–1.07) and SAEs (RR, 0.70; 95% CI, 0.45–1.08).

2.3.2. 1B: comparisons among drugs in biologic-naïve patients

> **Statement 2: For adults with moderate to severe, active UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using infliximab over adalimumab and golimumab for the induction of remission.** (*Conditional recommendation; very low-quality evidence – Agreement rate: 100%*)

Evidence on the choice between infliximab and adalimumab for patients with moderate to severe UC refractory to conventional therapy who are naïve to biologics comes from indirect treatment comparisons. This point, coupled with the serious inconsistency detected in the adalimumab trials, and the sparse data for SAEs, resulted in very low-quality evidence (PICO 07). Given these caveats, infliximab was superior to adalimumab for inducing clinical response (RR, 1.39; 95% CI, 1.13–1.70) and achieving mucosal healing (RR, 1.41; 95% CI, 1.12–1.79). Instead, adalimumab and placebo were comparable regarding clinical remission (RR, 1.56; 95% CI, 0.92–2.67), AEs (RR, 1.01; 95% CI, 0.89–1.15) and SAEs (RR, 0.96; 95% CI, 0.61–1.54).

Furthermore, the panel suggests that infliximab is superior to golimumab for inducing remission in biologic-naïve patients. This statement is based on an indirect comparison based on eight studies (PICO 08) that found, at induction, no difference between the two biologics in terms of clinical remission (RR, 1.11; 95% CI, 0.62–1.97) or clinical response (RR, 1.27; 95% CI, 0.95–1.69). The stud-

ies, however, demonstrated a higher chance of the critical outcome mucosal healing for infliximab than for golimumab (RR, 1.32; 95% CI, 1.01–1.73). They did not find differences in the risk of AEs (RR, 0.94; 95% CI, 0.78–1.13) or SAEs (RR, 1.15; 95% CI, 0.33–4.07). However, it should be noted that the overall quality of evidence is very low, for several reasons: the evidence comes from indirect treatment comparisons, there is serious imprecision (sparse data), and there is serious inconsistency detected in the trials of golimumab vs. placebo (regarding safety data).

> **Statement 3: For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using vedolizumab over adalimumab due to vedolizumab's superiority in maintaining remission.** (*Conditional recommendation; low-quality evidence for induction of remission; moderate-quality evidence for maintenance of remission – Agreement rate: 82%*)

The comparison between adalimumab and vedolizumab for inducing remission included direct evidence for nearly all outcomes, with the exception of mucosal healing. Thus, the quality of evidence is low (PICO 20). In particular, the RR for clinical remission was 0.85 (95% CI, 0.65–1.12), while the RR for mucosal healing was 0.75 (95% CI, 0.52–1.08). Of note, superiority of vedolizumab over adalimumab was detected regarding clinical response, but this is not a critical outcome (RR, 0.71, 95% CI 0.62–0.81). Furthermore, the rates of AEs and SAEs were similar for adalimumab and vedolizumab, with RRs of 1.10 (95% CI, 1.00–1.22) and 1.25 (95% CI, 0.86–1.83), respectively. However, although no clear superiority of either drug was reported for the outcomes at induction, there was evidence of superiority of vedolizumab for the maintenance of remission (PICO 42). This evidence comes from a phase 3b, double-blind, double-dummy, randomized, active-controlled trial (VARSITY) and regards the maintenance of both clinical remission (RR, 0.72; 95% CI, 0.57–0.91) and mucosal healing (RR, 0.70; 95% CI, 0.57–0.86). Of note, for corticosteroid-free remission, no significantly different rates were observed between the two drugs.

Panel comment beyond GRADE: The superiority of vedolizumab over adalimumab for maintaining remission was also found in a recent observational study [17].

> **Statement 4: For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD makes no recommendation on the use of:**
> - infliximab over vedolizumab, ustekinumab, or tofacitinib;
> - adalimumab over golimumab, ustekinumab, or tofacitinib;
> - golimumab over vedolizumab, ustekinumab, or tofacitinib;
> - vedolizumab over ustekinumab or tofacitinib;
> - ustekinumab over tofacinitib;
> (*No recommendation; low or very low-quality evidence – Agreement rate: 86%*)

Comparisons of infliximab to vedolizumab, ustekinumab and tofacitinib, in adults with moderate to severe UC naïve to biologics, are limited by imprecision and indirectness. Hence, there is very low-quality evidence in all cases (PICOs 18, 61, and 19, respectively). There were no differences between infliximab and vedolizumab for all outcomes, including clinical remission (RR, 1.08; 95% CI, 0.54–2.19), clinical response (RR, 1.09; 95% CI, 0.77–

1.56), mucosal healing (RR, 1.06; 95% CI, 0.74–1.53), AEs (RR, 1.05; 95% CI, 0.94–1.17), and SAEs (RR, 1.15; 95% CI, 0.59–2.26). Furthermore, there were no differences between infliximab and ustekinumab in terms of clinical remission (RR, 1.47; 95% CI, 0.74–2.92), clinical response (RR, 1.02; 95% CI, 0.77–1.36), mucosal healing (RR, 1.20; 95% CI, 0.79–1.82), AEs (RR, 1.06; 95% CI, 0.96–1.18), and SAEs (RR, 1.22; 95% CI, 0.66–2.28). Similarly, there were no differences between infliximab and tofacitinib in the induction of clinical remission (RR, 1.32; 95% CI, 0.74–2.37), clinical response (RR, 1.26; 95% CI, 0.97–1.64), mucosal healing (RR, 1.15; 95% CI, 0.76–1.72), AEs (RR, 1.07; 95% CI, 0.98–1.17), and SAEs (RR, 1.17; 95% CI, 0.69–1.99). Notably, for the maintenance of remission, infliximab was inferior to tofacitinib for both clinical remission (RR, 0.59; 95% CI, 0.36–0.97) and mucosal healing (RR, 0.56; 95% CI, 0.36–0.87) (PICO 41).

Panel comment beyond GRADE: The lack of a recommendation regarding the choice between infliximab and tofacitinib is based on data at induction only. However, the superiority of tofacitinib for the maintenance of remission (assessed without distinguishing between biologic-naïve and biologic-experienced patients) should be interpreted with caution, as it is derived from an indirect comparison, and the real-world experience with tofacitinib is currently limited.

The comparison between the two subcutaneous anti-TNF agents (adalimumab and golimumab) in UC patients naïve to biologics is based on indirect evidence. The lack of a recommendation arises from two points. On one hand, the quality of evidence is very low because of serious inconsistency, very serious indirectness, and serious imprecision (PICO 09). On the other hand, there were no differences between the drugs for the critical outcomes of clinical remission (RR, 0.71; 95% CI, 0.39–1.30), mucosal healing (RR, 0.94; 95% CI, 0.72–1.22) and SAEs (RR, 1.20; 95% CI, 0.33–4.29) and for the important, but not critical, outcomes of clinical response (RR, 0.91; 95% CI, 0.69–1.22) and AEs (RR, 0.93; 95% CI, 0.75–1.15).

Similarly, comparisons between adalimumab and both ustekinumab (PICO 62) and tofacitinib (PICO 21) also are based only on indirect evidence. In terms of inducing clinical remission, adalimumab was similar to both ustekinumab (RR, 0.94; 95% CI, 0.46–1.91) and tofacitinib (RR, 0.85; 95% CI, 0.46–1.56). In terms of mucosal healing, adalimumab was again similar to both ustekinumab (RR, 0.85; 95% CI, 0.56–1.29) and tofacitinib (RR, 0.81; 95% CI, 0.54–1.22). Of note, superiority of ustekinumab over adalimumab was detected regarding clinical response, but this is not a critical outcome (RR, 0.74; 95% CI, 0.56–0.98). Finally, there were no differences in safety outcomes: For AEs, similar risks were found between adalimumab and both ustekinumab (RR, 1.05; 95% CI, 0.91–1.22) and tofacitinib (RR, 1.06; 95% CI, 0.92–1.22). Similar risks were also found for SAEs between adalimumab and both ustekinumab (RR, 1.27; 95% CI, 0.66–2.45) and tofacitinib (RR, 1.21; 95% CI, 0.69–2.14).

Furthermore, the panel made no recommendation for the choice between golimumab and vedolizumab (PICO 22), ustekinumab (PICO 63), or tofacitinib (PICO 23) in adults with moderate to severe UC naïve to biologics. The evidence comes only from indirect comparisons between these drugs and is of very low quality overall, with serious or very serious imprecision due to sparse data, and serious inconsistency regarding AEs and SAEs in golimumab trials. A superiority of golimumab was not detected regarding efficacy and safety outcomes. Comparing golimumab to vedolizumab, ustekinumab, and tofacitinib, the RRs for clinical remission were 0.98 (95% CI, 0.46–2.09), 1.33 (95% CI, 0.63–2.80), and 1.19 (95% CI, 0.62–2.29), respectively. The corresponding RRs for mucosal healing were 0.80 (95% CI, 0.55–1.18), 0.90 (95% CI, 0.58–1.40), and 0.87 (95% CI, 0.57–1.33), respectively. The safety profiles were similar between golimumab and the other drugs: For all AEs, the risk with

golimumab was similar to those of vedolizumab (RR, 1.12, 95% CI, 0.92–1.37), ustekinumab (RR, 1.13, 95% CI, 0.93–1.38), and tofacitinib (RR, 1.14, 95% CI, 0.94–1.38). The SAEs risk with golimumab was also similar to those of vedolizumab (RR, 1.00, 95% CI, 0.26–3.91), ustekinumab (RR, 1.06, 95% CI, 0.28–4.06), and tofacitinib (RR, 1.01, 95% CI, 0.28–3.72).

Comparisons of vedolizumab to ustekinumab (PICO 64) and to tofacitinib (PICO 24) in biologic-naïve patients were based only on indirect evidence. As a result, the overall quality of evidence is very low, with serious or very serious imprecision due to sparse data. Differences between vedolizumab and ustekinumab were not detected regarding the outcomes of clinical remission (RR, 1.36; 95% CI, 0.58–3.15), clinical response (RR, 0.94; 95% CI, 0.62–1.40), mucosal healing (RR, 1.13; 95% CI, 0.68–1.87), AEs (RR, 1.01; 95% CI, 0.89–1.15), or SAEs (RR, 1.06; 95% CI, 0.47–2.39). Similarly, differences between vedolizumab and tofacitinib were not detected regarding clinical remission (RR, 1.22; 95% CI, 0.57–2.61), mucosal healing (RR, 1.08; 95% CI, 0.66–1.77), AEs (RR, 1.02; 95% CI, 0.90–1.15), and SAEs (RR, 1.01; 95% CI, 0.48–2.14).

Finally, for the comparison between tofacitinib and ustekinumab in biologic-naïve patients (PICO 65), very low-quality evidence was found, mainly due to very serious indirectness. No differences were found at induction between the drugs regarding clinical remission (RR, 1.11; 95% CI, 0.53–2.35), clinical response (RR, 0.81; 95% CI, 0.59–1.13), mucosal healing (RR, 1.05; 95% CI, 0.61–1.78), AEs (RR, 0.99; 95% CI, 0.88–1.11), or SAEs (RR, 1.05; 95% CI, 0.52–2.11). However, ustekinumab was better in the maintenance of clinical remission (RR, 0.54; 95% CI, 0.32–0.91) and of mucosal healing (RR, 0.57; 95% CI, 0.36–0.90), although the evidence comes only from indirect comparisons (PICO 50). Regarding safety outcomes during maintenance therapy, no significant differences were observed between the drugs regarding AEs (RR, 1.01; 95% CI, 0.90–1.14) or SAEs(RR, 0.96; 95% CI, 0.47–1.93) .

Panel comment beyond GRADE: The lack of a recommendation on the choice between ustekinumab and tofacitinib is based on data at induction only. However, the superiority of ustekinumab over tofacitinib for the maintenance of remission (assessed without distinguishing between biologic-naïve and biologic-experienced patients) should be interpreted with caution, as it is derived from an indirect comparison and the real-world experience with these drugs is currently limited.

2.3.3. 1C: biologics or tofacitinib vs. no treatment in biologic-experienced patients

> **Statement 5: For adults with moderate to severe, active UC refractory to at least one anti-TNF agent, IG-IBD makes no recommendation in favor of or against using infliximab or golimumab to induce remission.** (*No recommendation; knowledge gap – Agreement rate: 68%*)

Given that there is insufficient evidence to inform this specific question, IG-IBD is not able to make recommendations on the use of infliximab or golimumab for the induction of remission in patients previously found to be refractory to a different anti-TNF agent (PICOs 04 and 06, respectively).

Panel comment beyond GRADE: The 15-year clinical experience with infliximab and demonstration of this drug's efficacy against UC in observational studies [18,19] suggest that it may also be effective in patients in whom previous treatment with a different anti-TNF agent was unsuccessful. Clinical experience with golimumab is more limited, but there is evidence from observational studies of a clinical benefit in this setting [20,21].

> **Statement 6: For adults with moderate to severe UC refractory to at least one anti-TNF agent, IG-IBD suggests against using adalimumab or vedolizumab to induce remission.** (*Conditional recommendation; low-quality evidence - Agreement rate: 45%*)

IG-IBD suggests against using adalimumab or vedolizumab in adults with moderate to severe UC refractory to therapy with an anti-TNF agent. Regarding adalimumab, the recommendation is conditional due to the overall low quality of evidence (serious or very serious imprecision: efficacy data at 8 weeks are from a single study; PICO 05). In addition, adalimumab was not superior to placebo for any efficacy outcome, including clinical remission (RR, 1.33; 95% CI, 0.51–3.42), clinical response (RR, 1.28; 95% CI, 0.86–1.91), and mucosal healing (RR, 1.07; 95% CI, 0.68–1.68).

Similarly, serious or very serious imprecision due to sparse data resulted in low-quality evidence for vedolizumab (PICO 14). Vedolizumab was not superior to placebo for any efficacy outcome, including clinical remission (RR, 1.54; 95% CI, 0.50–4.76), clinical response (RR, 1.33; 95% CI, 0.66–2.69), and mucosal healing (RR, 1.15; 95% CI, 0.69–1.90).

Panel comment beyond GRADE: There is a clinical perception and evidence from observational studies [22–24] that a substantial proportion of patients previously found to be unresponsive to an anti-TNF drug have a clinical benefit with vedolizumab as a second-line agent. Nonetheless, the precise profile of such vedolizumab-responsive patients is not known. Similar considerations can be made for adalimumab as a second-line agent [25,26]. The low rate of agreement reported for this statement further raises doubts about the negative indication for adalimumab and vedolizumab in this setting.

> **Statement 7: For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission.** (*Strong recommendation; moderate-quality evidence for tofacitinib; low-quality evidence for ustekinumab – Agreement rate: 91%*)

IG-IBD recommends using tofacitinib or ustekinumab in adults with moderate to severe UC refractory to at least one biologic. The recommendation for tofacitinib is based on three studies with data on clinical remission and clinical response, two studies for mucosal healing, and four studies with data on AEs and SAEs (PICO 16). About efficacy, evidence was in favor of tofacitinib over placebo for the outcomes of induction of clinical remission (RR, 8.40; 95% CI, 1.93–36.57), clinical response (RR, 2.10; 95% CI, 1.53–2.88), and mucosal healing (RR, 3.43; 95% CI, 1.72–6.86). Notably, for safety, tofacitinib and placebo had similar risks of AEs (RR, 0.99; 95% CI, 0.92–1.07) and SAEs (RR, 0.70; 95% CI, 0.45–1.08). Quality of evidence is moderate due to serious imprecision (sparse data).

Regarding ustekinumab, efficacy outcomes were assessed by only one study at 8 weeks, while safety data at 8–52 weeks were extracted from two studies. The overall quality of evidence was judged to be low due to very serious imprecision (sparse data) on critical outcomes such as clinical remission and mucosal healing (PICO 17). Nonetheless, ustekinumab was superior to placebo for all efficacy outcomes, including induction of clinical remission (RR, 10.18; 95% CI, 2.43–42.73), clinical response (RR, 2.09; 95% CI, 1.58–2.78), and mucosal healing (RR, 3.09; 95% CI, 1.62–5.86). There were similar risks in AEs (RR, 1.00; 95% CI, 0.92–1.10) and SAEs (RR, 0.67; 95% CI, 0.39–1.17).

Panel comment beyond GRADE: Both tofacitinib and ustekinumab have proven to be effective and safe in this setting. However, robust real-world studies are needed to confirm the data from randomized controlled trials. In addition, the profiles of the ideal patient to be treated differ for the two drugs: tofacitinib should not be used in patients with thrombotic or cardiovascular risk factors, while ustekinumab is also indicated for frail patients due its safety profile.

2.3.4. 1D: comparisons among drugs in biologic-experienced patients

> **Statement 8: For adults with moderate to severe UC refractory to therapy with at least one biologic, IG-IBD makes no recommendation on the use of:**
> - infliximab over adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab;
> - adalimumab over golimumab;
> - golimumab over vedolizumab, tofacitinib, or ustekinumab.
>
> (*No recommendation; knowledge gap – Agreement rate: 91%*)

For adults with moderate to severe UC refractory to at least one biologic, the panel is not able to recommend a preferred drug for inducing remission, because there is insufficient supporting evidence. The analyses taken into consideration, but rejected, were a possible preferential use of infliximab over the drugs adalimumab (PICO 10), golimumab (PICO 11), vedolizumab (PICO 66), tofacitinib (PICO 69), or ustekinumab (PICO 72); a possible preferential use of adalimumab over golimumab (PICO 12); and a possible use of golimumab over vedolizumab (PICO 68), tofacitinib (PICO 71), or ustekinumab (PICO 78).

> **Statement 9: For adults with moderate to severe UC refractory to therapy with at least one biologic, IG-IBD makes no recommendation on the use of adalimumab over vedolizumab or on the use of tofacitinib over ustekinumab.** (*No recommendation; very low-quality evidence – Agreement rate: 91%*)

Evidence on the choice between adalimumab and vedolizumab for patients with moderate to severe UC who were already found refractory to biological therapy includes direct comparisons (PICO 67). However, the very serious indirectness for mucosal healing and imprecision for both mucosal healing and clinical remission resulted in very low-quality evidence. Vedolizumab was found to be superior on the important, but not critical, outcome of clinical response (RR, 0.58; 95% CI, 0.40–0.84), but neither on the critical outcomes of clinical remission (RR, 0.54; 95% CI, 0.27–1.10), mucosal healing (RR, 0.93; 95% CI, 0.47–1.84) and SAEs (RR, 1.25; 95% CI, 0.86–1.83), nor regarding AEs (RR, 1.10; 95% CI, 1.00–1.22). These data, combined with the low-quality evidence, made it impossible for the panel to recommend one drug over the other in this setting. As previously stated, there is direct evidence from the VARSITY study of superiority of vedolizumab over adalimumab for the maintenance of remission (PICO 42), even if the difference in clinical remission rates between the two biologics was not statistically significant among patients previously treated with an anti-TNF agent.

Similarly, for the comparison between tofacitinib and ustekinumab in biologic-experienced patients (PICO 75), very low-quality evidence was found, mainly due to very serious indirectness. There were no differences between the two drugs regarding

the efficacy outcomes of clinical remission (RR, 0.83; 95% CI, 0.11–6.43), clinical response (RR, 1.01; 95% CI, 0.66–1.54), or mucosal healing (RR, 1.11; 95% CI, 0.43–2.85), nor for the safety outcomes of AEs (RR, 0.99; 95% CI, 0.88–1.11) and SAEs (RR, 1.05; 95% CI, 0.52–2.11).

> **Statement 10: For adults with moderate to severe UC refractory to at least one biologic, IG-IBD suggests using tofacitinib or ustekinumab over adalimumab or vedolizumab.** (*Conditional recommendation; very low-quality evidence – Agreement rate: 55%*)

Evidence on the choice between adalimumab and either tofacitinib or ustekinumab for patients with moderate to severe UC refractory to at least one biologic comes from indirect treatment comparisons. This point, coupled with very serious imprecision, resulted in very low-quality evidence (PICOs 70 and 73). At induction, for clinical remission, adalimumab was inferior to tofacitinib (RR, 0.16; 95% CI, 0.03–0.91) and ustekinumab (RR, 0.13; 95% CI, 0.02–0.73). For the other critical outcome, namely achievement of mucosal healing, adalimumab was similarly inferior to both tofacitinib (RR, 0.31; 95% CI, 0.14–0.71) and ustekinumab (RR, 0.35; 95% CI, 0.16–0.76). No differences were seen in the risks of AEs between adalimumab and either tofacitinib (RR, 1.06; 95% CI, 0.92–1.22) or ustekinumab (RR, 1.05; 95% CI, 0.91–1.22). There were also no differences in the risks of SAEs between adalimumab and either tofacitinib (RR, 1.21; 95% CI, 0.69–2.14) or ustekinumab (RR, 1.27; 95% CI, 0.66–2.45). Notably, in the maintenance of remission, a difference in favor of tofacitinib was detected for mucosal healing (RR, 0.53; 95% CI, 0.33–0.86; PICO 44), while no differences were observed in the comparison between adalimumab and ustekinumab at maintenance (PICO 43).

Similarly, IG-IBD suggests using tofacitinib or ustekinumab over vedolizumab in patients with moderate to severe UC refractory to at least one biologic (PICOs 25 and 26). The overall quality of evidence is very low for several reasons: evidence only from indirect comparisons between different drugs, serious imprecision due to sparse data, serious inconsistency regarding clinical response in vedolizumab trials, and concerns over intransitivity (different proportions of participants with prior exposure to two or more biologics or to different classes of biologics). However, at induction, vedolizumab was inferior to tofacitinib regarding mucosal healing (RR, 0.34; 95% CI, 0.14–0.79), and it was inferior to ustekinumab for both clinical remission (RR, 0.15; 95% CI, 0.02–0.94) and mucosal healing (RR, 0.37; 95% CI, 0.16–0.84). Risks of AEs were similar between vedolizumab and both tofacitinib (RR, 1.02; 95% CI, 0.90–1.15) and ustekinumab (RR, 1.01; 95% CI, 0.89–1.15). SAE risks, too, were similar between vedolizumab and both tofacitinib (RR, 1.01; 95% CI 0.48–2.14) and ustekinumab (RR, 1.06; 95% CI 0.47–2.39).

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

> **Statement 11: For adults with moderate to severe UC refractory to conventional therapy, IG-IBD suggests using combination therapy with infliximab plus an immunosuppressant rather than infliximab monotherapy for the induction of remission.** (*Conditional recommendation; low quality evidence – Agreement rate: 55%*)

The panel suggests using combination therapy with infliximab plus an immunosuppressant instead of infliximab monotherapy in adults with moderate to severe UC refractory to conventional therapy (PICO 27). Because the evidence comes from only one study, there is serious imprecision due to sparse data, and the overall quality of evidence is low. Superiority of the combination therapy was detected for the critical outcome of clinical remission (RR, 1.80; 95% CI, 1.09–2.97), but not for clinical response (RR, 1.12; 95% CI, 0.92–1.36) or mucosal healing (RR, 1.15; 95% CI 0.88–1.50). The risks of AEs (RR, 1.12; 95% CI, 0.74–1.72) and SAEs (RR, 1.30; 95% CI, 0.30–5.62) were similar for the two strategies.

Panel comment beyond GRADE: This recommendation arises from only one study, which showed superiority of infliximab plus an immunosuppressant over infliximab monotherapy for a critical outcome (clinical remission). It should be noted that the primary endpoint of the study was set at 16 weeks. Therefore, the period of observation is limited, and there are safety concerns regarding prolonged combination therapy [27,28].

Statement 12: For adults with moderate to severe UC refractory to conventional therapy, IG-IBD makes no recommendation on using combination therapy with adalimumab plus an immunosuppressant vs. adalimumab monotherapy for the induction of remission. (*No recommendation; knowledge gap – Agreement rate: 95%*)

There panel was not able to formulate any recommendation on this point due to insufficient evidence.

2.5. Setting 3: acute severe UC refractory to intravenous steroids

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Statement 13: For adults with acute severe UC refractory to intravenous steroids, IG-IBD makes no recommendation on using infliximab vs. cyclosporine. (*No recommendation; very low-quality evidence – Agreement rate: 95%*)

IG-IBD makes no recommendation on using infliximab vs. cyclosporine in adults with acute severe UC refractory to intravenous steroids. The overall quality of evidence is very low for several reasons: the evidence comes from two studies at serious risk of bias (neither patients nor investigators were masked to the treatments), and there are serious inconsistency and very serious imprecision for mortality, and serious imprecision for SAEs. A superiority of infliximab over cyclosporine was not detected regarding efficacy or safety outcomes. The RRs for early and late colectomy were 1.00 (95% CI, 0.72–1.39) and 0.89 (95% CI, 0.70–1.13), respectively, while the risks of mortality (RR, 1.00; 95% CI, 0.02–45.2) and SAEs (RR, 1.17; 95% CI, 0.71–1.94) were similar between the drugs (PICO 29).

Panel comment beyond GRADE: Only one rescue therapy line (with infliximab or cyclosporine) should be attempted. A second administration of rescue therapy poses significant safety problems with a higher mortality risk [29–31] and is generally not recommended. However, it may be occasionally considered in selected cases at tertiary referral centers.

2.6. Setting 4: maintenance of remission induced by biologics or tofacitinib

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Statement 14: For adults with UC who achieved remission with infliximab, adalimumab, vedolizumab, ustek-

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inumab or tofacitinib, IG-IBD recommends using the same drug as maintenance treatment. (*Strong recommendation; high-quality evidence for infliximab; moderate-quality evidence for adalimumab, vedolizumab, ustekinumab, and tofacitinib – Agreement rate: 100%*)

IG-IBD recommends using infliximab as maintenance treatment in adults with UC that went into remission with this treatment (PICO 30). The statement is based on five studies that clearly showed that infliximab was superior to placebo in maintaining clinical remission (RR, 1.99; 95% CI, 1.52–2.59) and mucosal healing (RR, 1.76; 95% CI, 1.39–2.23). The risk of AEs was higher with infliximab (RR, 1.06; 95% CI 1.01–1.12), but the risk of SAEs was not (RR, 0.82; 95% CI, 0.61–1.10).

Similarly, the panel recommends using adalimumab as maintenance treatment in adults with UC who achieved remission with this drug, even if the evidence was judged to be moderate due to inconsistency on AEs (heterogeneity) and imprecision on clinical remission (sparse data; PICO 31). The statement is based on three studies which showed that adalimumab was superior to placebo in maintaining clinical remission (RR, 2.20; 95% CI, 1.44–3.35) and mucosal healing (RR, 1.68; 95% CI, 1.24–2.28). Furthermore, adalimumab and placebo posed similar risks of AEs (RR, 1.05; 95% CI, 0.94–1.19) and SAEs (RR, 0.85; 95% CI, 0.59–1.21).

Regarding vedolizumab, there is enough evidence to recommend it as maintenance treatment in adults with UC that went into remission with this drug. The statement is based on three studies that clearly showed that vedolizumab was superior to placebo in maintaining clinical remission (RR, 2.37; 95% CI, 1.74–3.23) and mucosal healing (RR, 2.35; 95% CI, 1.80–3.07). In the five studies that reported safety data, vedolizumab and placebo had similar risk of AEs (RR, 1.01; 95% CI, 0.92–1.11) and SAEs (RR, 0.71; 95% CI, 0.39–1.30). The overall quality of evidence is moderate due to serious imprecision in SAEs (PICO 33).

The panel recommends using ustekinumab as maintenance treatment in adults with UC who went into remission with this drug. The statement is based on one study that reported efficacy data and on two studies that reported safety data. Overall, ustekinumab was superior to placebo in maintaining clinical remission (RR, 1.82; 95% CI, 1.33–2.49) and mucosal healing (RR, 1.79; 95% CI, 1.36–2.36). Ustekinumab and placebo had similar risk of AEs (RR, 1.00; 95% CI, 0.92–1.10) and SAEs (RR, 0.67; 95% CI, 0.39–1.17). Serious imprecision (sparse data) in SAEs resulted in an overall moderate quality of evidence (PICO 35).

Finally, IG-IBD recommends using tofacitinib as maintenance treatment in adults with UC that went into remission with this drug. For efficacy, the statement is based on only one study that clearly showed that tofacitinib was superior to placebo for both clinical remission (RR, 3.37; 95% CI, 2.23–5.10) and mucosal healing (RR, 3.16; 95% CI, 2.17–4.61). For safety, according to four studies, tofacitinib and placebo had similar risk of both AEs (RR, 0.99; 95% CI, 0.92–1.07) and SAEs (RR, 0.70; 95% CI, 0.45–1.08). Serious imprecision in SAEs, due to sparse data, resulted in a moderate quality of evidence (PICO 34).

Statement 15: For adults with UC who achieved remission with golimumab, IG-IBD makes no recommendation on using golimumab as maintenance therapy. (*Conditional recommendation; low quality of evidence – Agreement rate: 55%*)

IG-IBD makes no recommendation on using golimumab in adults with UC who achieved remission with this drug. Evidence

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on efficacy outcomes comes only from two studies, while evidence on safety outcomes comes from three studies. The overall quality of evidence is low, with serious imprecision due to sparse data and serious inconsistency for all outcomes (PICO 32). Furthermore, superiority of golimumab over no treatment was not detected regarding efficacy or safety outcomes. Indeed, when comparing golimumab to placebo, the RRs for clinical remission and mucosal healing were 3.01 (95% CI, 0.60–15.1) and 2.27 (95% CI, 0.96–5.38), respectively. Golimumab and placebo posed similar risks of AEs (RR, 1.13; 95% CI, 0.95–1.35) and SAEs (RR, 0.71; 95% CI, 0.21–2.43).

Panel comment beyond GRADE: The failure to recommend golimumab as maintenance therapy resulted from the strict critical outcomes used to assess efficacy. However, it is reasonable to continue golimumab as a maintenance treatment in those cases of successful induction with golimumab.

2.7. Setting 5: optimization strategies and de-escalation of anti-TNF-based treatments

> **Statement 16: For adults with moderate to severe UC, IG-IBD makes no recommendation on using an anti-TNF agent plus an immunosuppressant vs. anti-TNF monotherapy as maintenance treatment.** (*No recommendation; very low-quality evidence for infliximab; knowledge gap for adalimumab and golimumab – Agreement rate: 86%*)

> **Statement 17: For adults with moderate to severe UC, IG-IBD makes no recommendation on using an anti-TNF agent plus an immunosuppressant vs. immunosuppressant monotherapy as maintenance treatment.** (*No recommendation; knowledge gap – Agreement rate: 82%*)

The panel makes no recommendation on using an anti-TNF agent (infliximab, adalimumab or golimumab) plus an immunosuppressant vs. anti-TNF monotherapy as maintenance treatment in adults with UC in remission (PICOs 51, 52, and 53). Only limited evidence comes from a single open-label, prospective, one-year, randomized controlled trial that compared a combination therapy (infliximab plus azathioprine) to infliximab monotherapy in a mixed population of IBD patients. In this study, no significant difference between treatments was observed in terms of clinical remission (RR, 1.19; 95% CI, 0.87–1.62). The quality of evidence is very low, and data were insufficient to explore differences in terms of mucosal healing, AEs or SAEs. Furthermore, no studies have investigated the efficacy and safety of combination therapy with adalimumab or golimumab plus an immunosuppressant versus the corresponding biologic monotherapy as maintenance treatment in UC patients. Finally, it is unknown how combination therapy with any anti-TNF agent (infliximab, adalimumab or golimumab) plus an immunosuppressant compares to immunosuppressant monotherapy as maintenance treatment (PICOs 54, 55, and 56).

> **Statement 18: For adults with UC who 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: knowledge gap – Agreement rate: 86%*)

> **Statement 19: For adults with UC who 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: 82%*)

IG-IBD makes no recommendation on using therapeutic drug monitoring or a standard symptom-based approach of dose optimization in patients who lost the response to anti-TNF agents (PICO 57). It also makes no recommendation on the choice between an anti-TNF agent plus immunosuppressant or a therapeutic change in patients who lost the response to anti-TNFs despite dose escalation (PICO 58).

Panel comment beyond GRADE: Although the evidence is insufficient to formulate recommendations, therapeutic drug monitoring, when available, can be considered a useful tool 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 [32].

> **Statement 20: For adults with UC who achieved long-term deep remission, IG-IBD makes no recommendation about the withdrawal of anti-TNF treatment.** (*No recommendation; very low-quality evidence – Agreement rate: 100%*)

The panel makes no recommendation about the withdrawal of anti-TNF treatment in adults with UC who achieved long-term deep remission. The only study that addressed this issue was a multicenter, open-label, randomized controlled trial conducted on 92 Japanese patients who achieved deep remission with infliximab (defined as corticosteroid-free remission for more than 6 months and a Mayo Endoscopic Subscore of 0 or 1). The study found that continuing anti-TNF treatment was marginally superior to withdrawing the drug in terms of maintaining clinical remission (RR, 0.68; 95% CI, 0.50–0.91). It is noteworthy that neither the patients nor the health care providers were masked to the randomization, which introduced a serious risk of bias. The study also sought evidence for other efficacy outcomes, such as maintenance of clinical response and mucosal healing, but the data were insufficient to draw any conclusion. No differences were observed between the infliximab-continued and infliximab-discontinued groups in terms of AEs (RR, 0.77; 95% CI, 0.29–2.04).

Panel comment beyond GRADE: The possibility of withdrawing treatment with 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. In case of withdrawal, remission can be maintained with 5-aminosalicylates or thiopurines [33,34]. However, the higher rate of clinical remission in patients who continue anti-TNF treatment and the risk of relapse in cases of discontinuation should always be considered.

3. Conclusions

Taken together, these 20 statements try to be a benchmark for clinicians dealing with ulcerative colitis (Table 3). The overall indication for clinical practice, however, should not arise only from the statement itself, but the statement should be integrated by the panel comment - where present - and by the agreement rate. In fact, the need to conceptually overcome in some points a certain "rigidity" of GRADE methodology emerged during both the drafting

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Table 3

Statements, quality of evidence, agreement rates, and panel comments beyond GRADE.

Statements	Quality of evidence	Agreement rate	Panel comment beyond GRADE
1. For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD recommends using infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib over no treatment to induce remission.	High-quality for infliximab and adalimumab; moderate-quality for vedolizumab and tofacitinib; low-quality for golimumab and ustekinumab	100%	The availability of low-cost biosimilars of infliximab and adalimumab – with proven, equivalent efficacy and safety to the originator products – reinforces the strength of the recommendation for these two biologics.
2. For adults with moderate to severe, active UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using infliximab over adalimumab and golimumab for the induction of remission.	Very low-quality	100%	
3. For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD suggests using vedolizumab over adalimumab due to vedolizumab's superiority in maintaining remission.	Low-quality for induction of remission; moderate-quality for maintenance of remission	82%	The superiority of vedolizumab over adalimumab for maintaining remission was also found in a recent observational study.
4. For adults with moderate to severe UC refractory to conventional therapy who are naïve to biologics, IG-IBD makes no recommendation on the use of: - infliximab over vedolizumab, ustekinumab, or tofacitinib; - adalimumab over golimumab, ustekinumab, or tofacitinib; - golimumab over vedolizumab, ustekinumab, or tofacitinib; - vedolizumab over ustekinumab or tofacitinib; - ustekinumab over tofacinitib.	Low- or very low-quality	86%	The lack of a recommendation regarding the choice between infliximab and tofacitinib is based on data at induction only. However, the reported superiority of tofacitinib for the maintenance of remission should be interpreted with caution, as it is derived from an indirect comparison, and the real-world experience with tofacitinib is currently limited. The lack of a recommendation on the choice between ustekinumab and tofacitinib is based on data at induction only. However, the superiority of ustekinumab over tofacitinib for the maintenance of remission should be interpreted with caution.
5. For adults with moderate to severe, active UC refractory to at least one anti-TNF agent, IG-IBD makes no recommendation in favor of or against using infliximab or golimumab to induce remission.	Knowledge gap	68%	The 15-year clinical experience with infliximab and demonstration of this drug's efficacy in observational studies suggest that it may also be effective in patients in whom previous treatment with a different anti-TNF agent was unsuccessful. Clinical experience with golimumab is more limited, but there is evidence from observational studies of a clinical benefit in this setting.
6. For adults with moderate to severe UC refractory to at least one anti-TNF agent, IG-IBD suggests against using adalimumab or vedolizumab to induce remission.	Low-quality	45%	There is a clinical perception and evidence from observational studies that a substantial proportion of patients previously found to be unresponsive to an anti-TNF drug have a clinical benefit with vedolizumab as a second-line agent. Similar considerations can be made for adalimumab as a second-line agent.
7. For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission.	Moderate-quality for tofacitinib; low-quality for ustekinumab	91%	Robust real-world studies are needed to confirm the data from randomized controlled trials. In addition, the profiles of the ideal patient to be treated differ for the two drugs: tofacitinib should not be used in patients with thrombotic or cardiovascular risk factors, while ustekinumab is also indicated for frail patients due its safety profile.
8. For adults with moderate to severe UC refractory to therapy with at least one biologic, IG-IBD makes no recommendation on the use of: - infliximab over adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab; - adalimumab over golimumab; - golimumab over vedolizumab, tofacitinib, or ustekinumab.	Knowledge gap	91%	
9. For adults with moderate to severe UC refractory to therapy with at least one biologic, IG-IBD makes no recommendation on the use of adalimumab over vedolizumab or on the use of tofacitinib over ustekinumab.	Very low-quality	91%	
10. For adults with moderate to severe UC refractory to at least one biologic, IG-IBD suggests using tofacitinib or ustekinumab over adalimumab or vedolizumab.	Very low-quality	55%	

Table 3 (*continued*)

Statements	Quality of evidence	Agreement rate	Panel comment beyond GRADE
11. For adults with moderate to severe UC refractory to conventional therapy, IG-IBD suggests using combination therapy with infliximab plus an immunosuppressant rather than infliximab monotherapy for the induction of remission.	Low-quality	55%	This recommendation arises from only one study. It should be noted that the primary endpoint of the study was set at 16 weeks. Therefore, the period of observation is limited, and there are safety concerns regarding prolonged combination therapy
12. For adults with moderate to severe UC refractory to conventional therapy, IG-IBD makes no recommendation on using combination therapy with adalimumab plus an immunosuppressant vs. adalimumab monotherapy for the induction of remission.	Knowledge gap	95%	
13. For adults with acute severe UC refractory to intravenous steroids, IG-IBD makes no recommendation on using infliximab vs. cyclosporine.	Very low-quality	95%	Only one rescue therapy line (with infliximab or cyclosporine) should be attempted. A second rescue therapy poses significant safety problems with a higher mortality risk and is generally not recommended. However, it may be occasionally considered in selected cases at tertiary referral centers.
14. For adults with UC who achieved remission with infliximab, adalimumab, vedolizumab, ustekinumab or tofacitinib, IG-IBD recommends using the same drug as maintenance treatment.	High-quality for infliximab; moderate-quality for adalimumab, vedolizumab, ustekinumab, and tofacitinib	100%	
15. For adults with UC who achieved remission with golimumab, IG-IBD makes no recommendation on using golimumab as maintenance therapy.	Low-quality	55%	The failure to recommend golimumab as maintenance therapy resulted from the strict critical outcomes used to assess efficacy. However, it is reasonable to continue golimumab as a maintenance treatment in those cases of successful induction with golimumab.
16. For adults with moderate to severe UC, IG-IBD makes no recommendation on using an anti-TNF agent plus an immunosuppressant vs. anti-TNF monotherapy as maintenance treatment.	Very low-quality evidence for infliximab; knowledge gap for adalimumab and golimumab	86%	
17. For adults with moderate to severe UC, IG-IBD makes no recommendation on using an anti-TNF agent plus an immunosuppressant vs. immunosuppressant monotherapy as maintenance treatment.	Knowledge gap	82%	
18. For adults with UC who 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.	Knowledge gap	86%	
19. For adults with UC who 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	82%	Therapeutic drug monitoring, when available, can be considered a useful tool to drive therapeutic choices in case of non-response or loss of response with anti-TNF agents.
20. For adults with UC who achieved long-term deep remission, IG-IBD makes no recommendation about the withdrawal of anti-TNF treatment.	Very low-quality	100%	This possibility should be assessed on a case-by-case basis and discussed with the patient. In case of withdrawal, remission can be maintained with 5-aminosalicylates or thiopurines. However, the higher rate of clinical remission in patients who continue anti-TNF treatment and the risk of relapse in cases of discontinuation should always be considered.

and revision of these guidelines. It should be acknowledged that it was not possible to formulate any recommendation for several statements. In such cases, values and preferences, safety, and the cost of the intervention should drive the choice of the most appropriate treatment. Furthermore, this underlines that the currently available evidence is not so robust to establish the positioning of each drug both as first and second (or more) lines of therapy, and that, pending new trials and head-to-head comparisons between drugs, real-world experience is necessary to complement the overall evidence.

Conflict of interest

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