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Guidelines

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

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ABSTRACT

The increased knowledge on the biological mechanisms underlying ulcerative colitis (UC) has triggered an advance in drug development, drastically changing the therapeutic landscape. Several biologics and small-molecule drugs have been regulatory approved (i.e., infliximab, adalimumab, golimumab, vedolizumab, ustekinumab and tofacitinib), and frequently pose clinical dilemmas: physicians need to know how these therapies can be used to optimize patient-important outcomes.

Adhering to the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methodology, this technical review systematically searched and identified the evidence, synthesized it using rigorous meta-analytic methodology, appraised its quality, and concisely presented it in a transparent way, forming the basis for developing clinical recommendations on the use of biologics and small-molecule drugs in adult patients with UC.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting the colon and the rectum [1,2]. It is characterized by mucosal inflammation, which is typically limited to the mucosal layer and causing superficial damage to the bowel wall [1,3]. Blood and/or mucus in the stool, urgency, tenesmus, incontinence, increased frequency of bowel movements, abdominal discomfort and fatigue are very common symptoms of UC, although fevers and weight loss can also be present in severe disease [4]. The exact pathogenesis of UC is still unknown; however, multiple factors, such as mucosal immune dysregulation, altered gut microbiota, genetic and environmental factors, have been implicated [5–8]. The diagnosis of the disease is made from a combination of clinical symptoms, endoscopic findings and histological analysis [9].

The choice of pharmacological therapy for patients with UC considers the level of disease activity (mild, moderate, or severe), the extent of the disease (proctitis, left-sided disease, extensive disease, or pancolitis), the course of the disease during follow-up, and patients' preferences [9]. Although most patients are treated successfully with a symptom-focused step-up approach comprising 5-ASA, corticosteroids and thiopurines, such as azathioprine and 6-mercaptopurine, a significant proportion of patients fail to improve. Importantly, a series of advanced treatments have emerged as a result of our improved understanding of the biologic mechanisms underlying UC. These include 5 biologic agents: infliximab (IFX), adalimumab (ADA), golimumab (GLM), vedolizumab (VDZ) and ustekinumab (UST), and one small-molecule drug: tofacitinib (TFB).

Due to the increasing availability of therapeutic options, there is considerable practice variability in the treatment of patients with UC. From the standpoint of patients and clinicians, having to select among several therapeutic alternatives poses a frequent clinical dilemma. This technical review synthesizes the evidence,

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appraises its quality, and forms the basis for developing clinical practice recommendations on the use of biologics and small-molecule drugs in UC.

2. Methods

2.1. Overview

This work used the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methodology [10,11]. We followed a stepwise process, which included: formulation of clinical questions; identification of patient-important outcomes (i.e. all outcomes that are important or critical to patients for decision making); systematic reviews of the literature; evidence synthesis for each outcome across studies; and grading of evidence quality for each patient-important outcome, followed by determining the overall quality of evidence across outcomes.

2.2. Formulation of clinical questions

Using the PICO system, which frames a clinical question by defining the specific Population (P), Intervention (I), Comparator (C), and Outcomes (O), we developed a total of 75 clinical questions (Appendix: List of PICO questions, pp. 7–16).

2.3. Outcomes of interest

The panelists were presented with the list of outcomes and asked to rate their importance through an online survey, by ranking each outcome on a scale from 1 to 9, based on the GRADE definitions [11]. Scores of 7–9 indicated an outcome that is critical to patients for decision making; scores of 4–6 indicated an important outcome, but not critical; and scores of 1–3 indicated an outcome of limited importance.

The panelists' agreement on outcomes' importance was assessed using the Disagreement Index (DI), as described in the RAND/UCLA appropriateness method [12]. The DI is based on the distribution and symmetry of the scores (across the scale from 1 to 9). A higher index indicates wider spread across the 9-point scale, while lower values indicate increasing consensus. If the DI is lower than 1.0, then there is no extreme variation (i.e. there is consensus). If the DI exceeds 1.0, then the distribution meets criteria for extreme variation in ratings.

Clinical remission, mucosal healing and serious adverse events (SAEs) were judged as critical outcomes for decision making across all clinical questions. Clinical response and adverse events (AEs) were considered important, but not critical. In the setting of acute severe UC, colectomy and mortality were judged as critical outcomes for decision making. There was consensus (DI<1.0) for all the outcomes. (Appendix: Classification of importance of outcomes, p. 17).

2.4. Literature search and study selection

A systematic search of PubMed, Embase and Scopus databases was first conducted on January 2020 (and was regularly updated through March 2021) to identify systematic reviews, meta-analyses and randomized controlled trials (RCTs) providing evidence to inform the clinical questions.

Results were exported and compiled into a common reference database using the Mendeley software. References were then deduplicated to derive a unique set of records. Two investigators (CP, DP) independently examined the search results and screened titles and abstracts to exclude any irrelevant reports. The full text of the selected publications was assessed for relevance, and their reference lists were examined to identify further articles. We also searched the ClinicalTrials.gov database to obtain details on study characteristics or outcomes, when these data were missing or unclearly presented in the original articles.

Overall, 5811 unique citations were identified (PubMed, 5045; Embase, 2681; and Scopus, 2198), 223 articles were retrieved for detailed evaluation, and, finally, 68 systematic reviews and/or meta-analyses and 40 RCTs were considered potentially relevant to our clinical questions.

A summary of the evidence search and selection process is reported in the Appendix (pp. 18–33), including a flowchart (p. 19), the list of the articles considered relevant to the development of the guidelines (pp. 20–25), and the list of publications excluded, with the reasons for exclusion (pp. 26–32). The search algorithms, for each one of the databases, are also presented (p. 33).

The totality of evidence informing these guidelines comes from randomized, placebo-controlled trials, or head-to-head trials, assessing biologics and small-molecule drugs in adult patients with UC.

2.5. Data abstraction and quality assessment of primary studies

Two reviewers (CP, SB) independently extracted the following information from the primary trials: publication data, trial's acronym, first author's last name, geographical location and year of publication, study design and length of follow-up, number of participants, population characteristics, intervention parameters including drug, dosage and administration, as well as efficacy and safety outcome data. Different dosages of the same drug were treated as different interventions, and we considered only data for dosage and administration as approved in the respective Summary of Product Characteristics.

The two reviewers independently assessed risk-of-bias (RoB) in included studies using the Cochrane Collaboration's tool [13], which addresses six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias (e.g. extreme baseline imbalances in prognostic factors). These items were classified as "low RoB", "high RoB", or "uncertain RoB". The trials judged to be at low risk in all six domains were classified as "low RoB", while those at high risk in at least one domain were classified as "high RoB".

Any disagreements, regarding data extraction or RoB assessment, were discussed with a third reviewer (DP) and resolved by consensus.

2.6. Data synthesis and statistical analysis

The risk ratio (RR) was used to measure treatment effects in all comparisons. Study-level RRs with 95% confidence intervals (CIs) were calculated in accordance with the intention-to-treat (ITT) principle. When zero events occurred in one group of a trial, we used a continuity correction that was inversely proportional to the relative size of the opposite group. In particular, the continuity correction for the treatment group was $1/(R+1)$, where R is the ratio of control group to treatment group sizes. Similarly, the continuity correction for the control group was $R/(R+1)$. This approach is superior than using a constant continuity correction of 0.5 in settings of sparse data and imbalanced study groups [14].

To synthesize the evidence for direct comparisons, we prepared forest plots and calculated the pooled effect estimates using random-effects models (DerSimonian and Laird approach) [15]. The between-study heterogeneity was examined using the Cochran's Q test [16] with a 0.10 level of significance, and the I-squared metric [17] with values>50% being considered as suggestive of significant heterogeneity. Publication bias could be assessed using funnel

plots, as well as the Begg's and Egger's tests [18,19], when there were at least 10 studies included in the meta-analysis.

To inform comparative efficacy and safety of different drugs when direct evidence was lacking, we first examined the conceptual homogeneity across trials (i.e. study designs, populations, and outcomes) and used the Bucher's method of adjusted indirect comparisons [20]. According to this statistical method, the placebo arm of each trial (i.e. the common comparator) is used as a "bridge" to perform a so-called "adjusted indirect treatment comparison (ITC)" of the investigational treatment arms.

To study harms (i.e. AEs and SAEs), we pooled randomized data from induction and maintenance trials, and for all participants (i.e. those with and those without previous exposure to biological agents).

For analyses of direct comparisons, we used the R software [21]. To determine the indirect evidence of pairwise contrasts that have not been directly compared, we used the ITC software (Indirect Treatment Comparison program, Canadian Agency for Drugs and Technologies in Health, Ontario, Canada) [22]. All p-values are two-tailed. For all tests (except for heterogeneity), a p-value less than 0.05 indicates statistical significance.

2.7. Estimating absolute magnitude of benefits and harms

To calculate absolute benefits and harms, we relied on the pooled event rates in the control groups. The absolute effect (i.e. the number of fewer or more events in the intervention group as compared to the control group) was based on the pooled risk ratio and the baseline risk in the control groups.

2.8. Quality of evidence

The quality of evidence was expressed using four categories: high, moderate, low, and very low [10,11]. For each clinical question, we first rated the quality of evidence separately for each patient-important outcome, and then determined an overall quality of evidence across outcomes. The quality of evidence demonstrates the certainty in the body of evidence (i.e. the confidence we have in the effect estimate). For a guideline panel, the quality of evidence reflects the extent to which the confidence in the effect estimate is adequate to support a particular recommendation [10,11].

To determine the quality of the evidence for each outcome across all studies (i.e. the body evidence), we started with rating direct evidence from RCTs as "high" quality, and then assessed five factors that could lead to rating down the quality of evidence:

- Risk of bias, i.e. limitations in study design or execution. It was assessed with the Cochrane's tool [13] as described above.
- Inconsistency, i.e. unexplained heterogeneity in results. It was assessed with the Cochran's Q test [16] with a 0.10 significance level, and the I-squared metric [17] with values$>$ 50% suggesting inconsistency. In case of inconsistency, the quality of evidence was downgraded by one level.
- Indirectness of evidence, i.e. addressing a different but related population, intervention, or outcome, from the one of interest. Moreover, when there were no direct comparisons between two interventions (i.e. no pairwise meta-analysis was feasible), we first examined the conceptual homogeneity across RCTs and, then, applied the Bucher's method of adjusted indirect comparisons [20]. The quality of evidence coming from the adjusted ITC was downgraded by two levels for indirectness.
- Imprecision. It characterizes the evidence coming from studies with few participants and few events, and thus having wide CIs around the effect estimates. We based our decision on the number of events. In direct comparisons, the quality of evidence was downgraded by one level when the total number of events was $<$ 100, and by two levels when it was $<$ 50. In contrast, when the comparison was indirect, the quality of evidence was downgraded by one level when the total number of events was $<$300, and by two levels when it was $<$ 150.
- Publication bias, that is an over- or under-estimation of the true effect due to selective publication of studies. It could be assessed using funnel plots, as well as the Begg's and the Egger's tests [18,19], only if there were at least ten studies included in the meta-analysis.

The overall quality of evidence was a combined rating of the quality of evidence across all outcomes considered critical for decision-making: the lowest quality of evidence for any of the critical outcomes determined the overall quality of evidence.

Our judgement, regarding the quality of evidence identified and synthesized for each clinical question, was detailed in the respective evidence tables (Appendix: Summary of Findings tables, pp. 34–240).

2.9. Summary-of-findings tables and evidence-to-decision framework

To present the evidence in a quick and accessible format, we used Summary-of-Findings (SoF) tables. They included the list of outcomes (and their relative importance for decision-making); the number of participants, the number of studies synthesized, and the length of follow-up; our judgements about each one of the quality of evidence factors examined (i.e. risk of bias, inconsistency, indirectness, imprecision, and publication bias), and the rating of quality of evidence for each one of the outcomes; the risk with control group (i.e. baseline risk); the risk with intervention group (i.e. risk of outcome in treated patients); the meta-analytic effect estimate (risk ratio); the anticipated absolute effects (i.e. the number of fewer or more events in treated patients, based on the effect estimate and baseline risk); and footnotes including the trials' references, explanations about information in the SoF table, and the overall quality of evidence across outcomes (Appendix: Summary of Findings tables, pp. 34–240).

For determining the direction and the strength of each recommendation, the guideline panel took into account the balance of desirable and undesirable consequences of the compared treatment options, the quality of evidence, and assumptions about values and preferences associated with the decision. Importantly, patient preferences with respect to mode, frequency, and place of administration, play a role in deciding which treatment to use, especially when different therapies appear to have similar efficacy and safety. Matching treatment attributes to patient preferences is associated with increased satisfaction and adherence, and with improved health-related quality of life. However, preferences vary among individuals. Systematic studies of patient preferences are rather limited in the field of UC, and the uncertainty concerning preferences, and their variability among individuals, might make a weak recommendation more likely (as it is less likely that a single recommendation would apply uniformly across all patients, and the right course of action is likely to differ between patients). Given the sparse study of patient preferences, the panel's experience with UC patients provided considerable insight. The panel also considered the extent of resource use associated with alternative treatment options [11].

3. Results

Evidence from 23 RCTs [23–45] was extracted, appraised, synthesized and presented in SoF tables (Appendix: pp. 34–240). It formed the basis for the evidence summaries reported below.

Overall, 23 of 75 clinical questions (31%) were informed by direct, head-to-head comparisons (with the quality of the respective

evidence judged: high [n = 3], moderate [n = 8], low [n = 8], and very low [n = 4]); 33 clinical questions (44%) were informed by indirect evidence (it was generated using the Bucher's method of adjusted indirect treatment comparisons: it was judged as of very low quality in all cases); while the evidence for 19 clinical questions (25%) was insufficient (i.e. data to complete the SoF table were not available).

PICO question 01: *Should we recommend IFX in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [23–26]. IFX (5 mg/kg IV) was superior to placebo for induction of clinical remission (RR: 2.72, 95% CI: 1.90–3.88; Figure 01a), clinical response (RR: 1.90, 95% CI: 1.64–2.20; Figure 01b) and mucosal healing (RR: 1.88, 95% CI: 1.59–2.23; Figure 01c) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic drug. The occurrence of AEs was increased with IFX (RR: 1.06, 95% CI: 1.01–1.12; Figure 01d), while for SAEs there was no significant difference (RR: 0.82, 95% CI: 0.61–1.10; Figure 01e). (Appendix: pp. 34–39; Overall quality of evidence: High).

PICO question 02: *Should we recommend ADA in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [27–29]. ADA (160/80/40 mg SC) was superior to placebo for induction of clinical remission (RR: 1.74, 95% CI: 1.17–2.59; Figure 02a), clinical response (RR: 1.37, 95% CI: 1.19–1.58; Figure 02b) and mucosal healing (RR: 1.33, 95% CI: 1.13–1.56; Figure 02c) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. The occurrence of AEs (RR: 1.05, 95% CI: 0.94–1.19; Figure 02d) and SAEs (RR: 0.85, 95% CI: 0.59–1.21; Figure 02e) did not differ. (Appendix: pp. 40–45; Overall quality of evidence: High).

PICO question 03: *Should we recommend GLM in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [30–32]. GLM (200/100 mg SC) was superior to placebo for induction of clinical remission (RR: 2.46, 95% CI: 1.56–3.89; Figure 03a), clinical response (RR: 1.50, 95% CI: 1.17–1.92; Figure 03b) and mucosal healing (RR: 1.42, 95% CI: 1.15–1.75; Figure 03c) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. The occurrence of AEs (RR: 1.13, 95% CI: 0.95–1.35; Figure 03d) and SAEs (RR: 0.71, 95% CI: 0.21–2.43; Figure 03e) did not differ. (Appendix: pp. 46–51; Overall quality of evidence: Low).

PICO question 04: *Should we recommend IFX in adult patients with moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 52).

PICO question 05: *Should we recommend ADA in adult patients with moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent?*
Evidence summary: Direct evidence from RCTs was synthesized [27–29]. ADA (160/80/40 mg SC) was not more effective than placebo for induction of clinical remission (RR: 1.33, 95% CI: 0.51–3.42; Figure 05a), clinical response (RR: 1.28, 95% CI: 0.86–1.91; Figure 05b) and mucosal healing (RR: 1.07, 95% CI: 0.68–1.68; Figure 05c) in moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent. The occurrence of AEs (RR: 1.05, 95% CI: 0.94–1.19; Figure 05d) and SAEs (RR: 0.85, 95% CI: 0.59–1.21; Figure 05e) was not different. (Appendix: pp. 53–58; Overall quality of evidence: Low).

PICO question 06: *Should we recommend GLM in adult patients with moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 59).

PICO question 07: *Should we recommend IFX or ADA in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [23–29]. IFX (5 mg/kg IV) was superior to ADA (160/80/40 mg SC) for induction of clinical response (RR: 1.39, 95% CI: 1.13–1.70) and mucosal healing (RR: 1.41, 95% CI: 1.12–1.79) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. We did not find any significant difference 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). (Appendix: pp. 60–61; Overall quality of evidence: Very low).

PICO question 08: *Should we recommend IFX or GLM in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [23–26, 30–32]. IFX (5 mg/kg IV) was superior to GLM (200/100 mg SC) for induction of mucosal healing (RR: 1.32, 95% CI: 1.01–1.73) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. We did not find any difference between IFX and GLM regarding clinical remission (RR: 1.11, 95% CI: 0.62–1.97), clinical response (RR: 1.27, 95% CI: 0.95–1.69), AEs (RR: 0.94, 95% CI: 0.78–1.13) and SAEs (RR: 1.15, 95% CI: 0.33–4.07). (Appendix: pp. 62–63; Overall quality of evidence: Very low).

PICO question 09: *Should we recommend ADA or GLM in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [27–32]. We did not find any significant difference between ADA (160/80/40 mg SC) and GLM (200/100 mg SC) regarding clinical remission (RR: 0.71, 95% CI: 0.39–1.30), clinical response (RR: 0.91, 95% CI: 0.69–1.22), mucosal healing (RR: 0.94, 95% CI: 0.72–1.22), AEs (RR: 0.93, 95% CI: 0.75–1.15) and SAEs (RR: 1.20, 95% CI: 0.33–4.29) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. (Appendix: pp. 64–65; Overall quality of evidence: Very low).

PICO question 10: *Should we recommend IFX or ADA in adult patients with moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 66).

PICO question 11: *Should we recommend IFX or GLM in adult patients with moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 67).

PICO question 12: *Should we recommend ADA or GLM in adult patients with moderately-to-severely active UC refractory to a previous therapy with an anti-TNF agent?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 68).

PICO question 13: *Should we recommend VDZ in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [33–35]. VDZ (300 mg IV) was superior to placebo for induction of clinical remission (RR: 2.51, 95% CI: 1.37–4.60; Figure 13a), clinical response (RR: 1.74, 95% CI: 1.26–2.40; Figure 13b) and mucosal healing (RR: 1.77, 95% CI: 1.28–2.45; Figure 13c) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic drug. The occurrence of AEs (RR: 1.01, 95% CI: 0.92–1.11; Figure 13d) and SAEs (RR: 0.71, 95% CI: 0.39–1.30; Figure 13e) did not differ. (Appendix: pp. 69–74; Overall quality of evidence: Moderate).

PICO question 14: *Should we recommend VDZ in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [33–35]. We did not find evidence that VDZ (300 mg IV) is more effective than placebo for induction of clinical remission (RR: 1.54, 95% CI: 0.50–4.76; Figure 14a), clinical response (RR: 1.33, 95% CI: 0.66–2.69; Figure 14b) and mucosal healing (RR: 1.15, 95% CI: 0.69–1.90; Figure 14c) in moderately-to-severely active UC refractory to at least one biologic. The occurrence of AEs (RR: 1.01, 95% CI: 0.92–1.11; Figure 14d) and SAEs (RR: 0.71, 95% CI: 0.39–1.30; Figure 14e) was not different. (Appendix: pp. 75–80; Overall quality of evidence: Low).

PICO question 15: *Should we recommend TFB in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [36,37]. TFB (10 mg PO) was superior to placebo for induction of clinical remission (RR: 2.06, 95% CI: 1.30–3.28; Figure 15a), clinical response (RR: 1.51, 95% CI: 1.21–1.87; Figure 15b) and mucosal healing (RR: 1.64, 95% CI: 1.13–2.37; Figure 15c) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic drug. The occurrence of AEs (RR: 0.99, 95% CI: 0.92–1.07; Figure 15d) and SAEs (RR: 0.70, 95% CI: 0.45–1.08; Figure 15e) did not differ. (Appendix: pp. 81–86; Overall quality of evidence: Moderate).

PICO question 16: *Should we recommend TFB in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [36,37]. TFB (10 mg PO) was superior to placebo for induction of clinical remission (RR: 8.40, 95% CI: 1.93–36.57; Figure 16a), clinical response (RR: 2.10, 95% CI: 1.53–2.88; Figure 16b) and mucosal healing (RR: 3.43, 95% CI: 1.72–6.86; Figure 16c) in moderately-to-severely active UC refractory to at least one biologic. The occurrence of AEs (RR: 0.99, 95% CI: 0.92–1.07; Figure 16d) and SAEs (RR: 0.70, 95% CI: 0.45–1.08; Figure 16e) was not different. (Appendix: pp. 87–92; Overall quality of evidence: Moderate).

PICO question 17: *Should we recommend UST in adult patients with moderately-to-severely active UC refractory to at least one anti-TNF agent?*
Evidence summary: Direct evidence from RCTs was synthesized [38]. UST (6 mg/kg IV) was superior to placebo for induction of clinical remission (RR: 10.18, 95% CI: 2.43–42.73; Figure 17a), clinical response (RR: 2.09, 95% CI: 1.58–2.78; Figure 17b) and mucosal healing (RR: 3.09, 95% CI: 1.62–5.86; Figure 17c) in moderately-to-severely active UC refractory to at least one anti-TNF agent. The occurrence of AEs (RR: 1.00, 95% CI: 0.92–1.10; Figure 17d) and SAEs (RR: 0.67, 95% CI: 0.39–1.17; Figure 17e) did not differ. (Appendix: pp. 93–98; Overall quality of evidence: Low).

PICO question 18: *Should we recommend IFX or VDZ in adult patients with moderately-to-severely active UC naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [23–26, 33–35]. We did not find any significant difference between IFX (5 mg/kg IV) and VDZ (300 mg IV) regarding 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) in moderately-to-severely active UC naïve to any biologic. (Appendix: pp. 99–100; Overall quality of evidence: Very low).

PICO question 19: *Should we recommend IFX or TFB in adult patients with moderately-to-severely active UC naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [23–26,36,37]. We did not find any significant difference between IFX (5 mg/kg IV) and TFB (10 mg PO) regarding 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) in moderately-to-severely active UC naïve to any biologic. (Appendix: pp. 101–102; Overall quality of evidence: Very low).

PICO question 20: *Should we recommend ADA or VDZ in adult patients with moderately-to-severely active UC naïve to any biologic?*
Evidence summary: Direct evidence from one RCT was considered [39]. ADA (160/80/40 mg SC) was inferior to VDZ (300 mg IV) for induction of clinical response (RR: 0.71, 95% CI: 0.62–0.81; Figure 20b) in moderately-to-severely active UC naïve to any biologic drug. However, there was not any difference regarding clinical remission (RR: 0.85, 95% CI: 0.65–1.12; Figure 20a), AEs (RR: 1.10, 95% CI: 1.00–1.22; Figure 20c) and SAEs (RR: 1.25, 95% CI: 0.86–1.83; Figure 20d). Also, using an adjusted ITC approach [27–29,33,34], we did not find any difference regarding mucosal healing (RR: 0.75, 95% CI: 0.52–1.08). (Appendix: pp. 103–107; Overall quality of evidence: Low).

PICO question 21: *Should we recommend ADA or TFB in adult patients with moderately-to-severely active UC naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [27–29,36,37]. We did not find any significant difference between ADA (160/80/40 mg SC) and TFB (10 mg PO) regarding clinical remission (RR: 0.85, 95% CI: 0.46–1.56), clinical response (RR: 0.91, 95% CI: 0.70–1.18), mucosal healing (RR: 0.81, 95% CI: 0.54–1.22), AEs (RR: 1.06, 95% CI: 0.92–1.22) and SAEs (RR: 1.21, 95% CI: 0.69–2.14) in moderately-to-severely active UC naïve to any biologic. (Appendix: pp. 108–109; Overall quality of evidence: Very low).

PICO question 22: *Should we recommend GLM or VDZ in adult patients with moderately-to-severely active UC naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [30–35]. We did not find any difference between GLM (200/100 mg SC) and VDZ (300 mg IV) regarding clinical remission (RR: 0.98, 95% CI: 0.46–2.09), clinical response (RR: 0.86, 95% CI: 0.57–1.29), mucosal healing (RR: 0.80, 95% CI: 0.55–1.18), AEs (RR: 1.12, 95% CI: 0.92–1.37) and SAEs (RR: 1.00, 95% CI: 0.26–3.91) in moderately-to-severely active UC naïve to any biologic. (Appendix: pp. 110–111; Overall quality of evidence: Very low).

PICO question 23: *Should we recommend GLM or TFB in adult patients with moderately-to-severely active UC naïve to any biologic?*

Evidence summary: An adjusted ITC was performed [30–32,36,37]. We did not find any difference between GLM (200/100 mg SC) and TFB (10 mg PO) regarding clinical remission (RR: 1.19, 95% CI: 0.62–2.29), clinical response (RR: 0.99, 95% CI: 0.71–1.38), mucosal healing (RR: 0.87, 95% CI: 0.57–1.33), AEs (RR: 1.14, 95% CI: 0.94–1.38) and SAEs (RR: 1.01, 95% CI: 0.28–3.72) in moderately-to-severely active UC naïve to any biologic. (Appendix: pp. 112–113; Overall quality of evidence: Very low).

PICO question 24: *Should we recommend VDZ or TFB in adult patients with moderately-to-severely active UC naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [33–37]. We did not find any difference between VDZ (300 mg IV) and TFB (10 mg PO) regarding clinical remission (RR: 1.22, 95% CI: 0.57–2.61), clinical response (RR: 1.15, 95% CI: 0.78–1.70), 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) in moderately-to-severely active UC naïve to any biologic. (Appendix: pp. 114–115; Overall quality of evidence: Very low).

PICO question 25: *Should we recommend VDZ or TFB in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: An adjusted ITC was performed [33–37]. VDZ (300 mg IV) was inferior to TFB (10 mg PO) for induction of mucosal healing (RR: 0.34, 95% CI: 0.14–0.79) in moderately-to-severely active UC refractory to at least one biologic. However, we did not find any significant difference regarding clinical remission (RR: 0.18, 95% CI: 0.03–1.17), clinical response (RR: 0.63, 95% CI: 0.29–1.37), AEs (RR: 1.02, 95% CI: 0.90–1.15) and SAEs (RR: 1.01, 95% CI: 0.48–2.14). (Appendix: pp. 116–117; Overall quality of evidence: Very low).

PICO question 26: *Should we recommend VDZ or UST in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: An adjusted ITC was performed [33–35,38]. VDZ (300 mg IV) was inferior to UST (6 mg/kg IV) for induction of clinical remission (RR: 0.15, 95% CI: 0.02–0.94) and mucosal healing (RR: 0.37, 95% CI: 0.16–0.84) in moderately-to-severely active UC refractory to at least one biologic. However, we did not find any significant difference regarding clinical response (RR: 0.64, 95% CI: 0.30–1.36), AEs (RR: 1.01, 95% CI: 0.89–1.15) and SAEs (RR: 1.06, 95% CI: 0.47–2.39). (Appendix: pp. 118–119; Overall quality of evidence: Very low).

PICO question 27: *Should we recommend IFX plus immunosuppressant (azathioprine [AZA] or methotrexate [MTX]) or IFX monotherapy in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from one RCT was used [40]. IFX plus immunosuppressant was superior to IFX monotherapy for induction of clinical remission (RR: 1.80, 95% CI: 1.09–2.97; Figure 27a) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. However, there was no difference regarding clinical response (RR: 1.12, 95% CI: 0.92–1.36; Figure 27b), mucosal healing (RR: 1.15, 95% CI: 0.88–1.50; Figure 27c), AEs (RR: 1.12, 95% CI: 0.74–1.72; Figure 27d) and SAEs (RR: 1.30, 95% CI: 0.30–5.62; Figure 27e). (Appendix: pp. 120–125; Overall quality of evidence: Low).

PICO question 28: *Should we recommend ADA plus immunosuppressant (AZA or MTX) or ADA monotherapy in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 126).

PICO question 29: *Should we recommend IFX or cyclosporine as first-line rescue therapy in adult patients with acute severe UC refractory to intravenous steroids?*
Evidence summary: Direct evidence from RCTs was synthesized [41–43]. IFX was not more effective than cyclosporine, as first-line rescue therapy in acute severe UC refractory to intravenous steroids, for any of the outcomes: early colectomy (RR: 1.00, 95% CI: 0.72–1.39; Figure 29a), late colectomy (RR: 0.89, 95% CI: 0.70–1.13; Figure 29b), mortality (RR: 1.00, 95% CI: 0.02–45.2; Figure 29c) and SAEs (RR: 1.17, 95% CI: 0.71–1.94; Figure 29d). (Appendix: pp. 127–131; Overall quality of evidence: Very low).

PICO question 30: *Should we recommend IFX as maintenance treatment in adult patients with UC achieving remission with IFX?*
Evidence summary: Direct evidence from RCTs was synthesized [23–26]. IFX (5 mg/kg IV q8w) was superior to placebo for maintenance of clinical remission (RR: 1.99, 95% CI: 1.52–2.59; Figure 30a) and mucosal healing (RR: 1.76, 95% CI: 1.39–2.23; Figure 30b) in adult patients with UC in remission. The occurrence of AEs was increased with IFX (RR: 1.06, 95% CI: 1.01–1.12; Figure 30c), while for SAEs there was no significant difference (RR: 0.82, 95% CI: 0.61–1.10; Figure 30d). (Appendix: pp. 132–136; Overall quality of evidence: High).

PICO question 31: *Should we recommend ADA as maintenance treatment in adult patients with UC achieving remission with ADA?*
Evidence summary: Direct evidence from RCTs was synthesized [27–29]. ADA (40 mg SC eow) was superior to placebo for maintenance of clinical remission (RR: 2.20, 95% CI: 1.44–3.35; Figure 31a) and mucosal healing (RR: 1.68, 95% CI: 1.24–2.28; Figure 31b) in patients with UC in remission. The occurrence of AEs (RR: 1.05, 95% CI: 0.94–1.19; Figure 31c) and SAEs (RR: 0.85, 95% CI: 0.59–1.21; Figure 31d) was not different. (Appendix: pp. 137–141; Overall quality of evidence: Moderate).

PICO question 32: *Should we recommend GLM as maintenance treatment in adult patients with UC achieving remission with GLM?*
Evidence summary: Direct evidence from RCTs was synthesized [30–32]. GLM (100 mg SC q4w) was not found superior to placebo for maintenance of clinical remission (RR: 3.01, 95% CI: 0.60–15.12; Figure 32a) and mucosal healing (RR: 2.27, 95% CI: 0.96–5.38; Figure 32b) in adults with UC in remission. The occurrence of AEs (RR: 1.13, 95% CI: 0.95–1.35; Figure 32c) and SAEs (RR: 0.71, 95% CI: 0.21–2.43; Figure 32d) did not differ. (Appendix: pp. 142–146; Overall quality of evidence: Low).

PICO question 33: *Should we recommend VDZ as maintenance treatment in adult patients with UC achieving remission with VDZ?*
Evidence summary: Direct evidence from RCTs was synthesized [33–35]. VDZ (300 mg IV q8w) was superior to placebo for maintenance of clinical remission (RR: 2.37, 95% CI: 1.74–3.23; Figure 33a) and mucosal healing (RR: 2.35, 95% CI: 1.80–3.07; Figure 33b) in adults with UC in remission. The occurrence of AEs (RR: 1.01, 95% CI: 0.92–1.11; Figure 33c) and SAEs (RR: 0.71, 95% CI: 0.39–1.30; Figure 33d) was not different. (Appendix: pp. 147–151; Overall quality of evidence: Moderate).

PICO question 34: *Should we recommend TFB as maintenance treatment in adult patients with UC achieving remission with TFB?*
Evidence summary: Direct evidence from RCTs was synthesized [36,37]. TFB (5 mg or 10 mg PO bid) was superior to placebo for maintenance of clinical remission (RR: 3.37, 95% CI: 2.23–5.10;

Figure 34a) and mucosal healing (RR: 3.16, 95% CI: 2.17–4.61; Figure 34b) in adult patients with UC in remission. The occurrence of AEs (RR: 0.99, 95% CI: 0.92–1.07; Figure 34c) and SAEs (RR: 0.70, 95% CI: 0.45–1.08; Figure 34d) did not differ. (Appendix: pp. 152–156; Overall quality of evidence: Moderate).

PICO question 35: *Should we recommend UST as maintenance treatment in adult patients with UC achieving remission with UST?*
Evidence summary: Direct evidence from RCTs was synthesized [38]. UST (90 mg SC q8w) was superior to placebo for maintenance of clinical remission (RR: 1.82, 95% CI: 1.33–2.49; Figure 35a) and mucosal healing (RR: 1.79, 95% CI: 1.36–2.36; Figure 35b) in adults with UC in remission. The occurrence of AEs (RR: 1.00, 95% CI: 0.92–1.10; Figure 35c) and SAEs (RR: 0.67, 95% CI: 0.39–1.17; Figure 35d) did not differ. (Appendix: pp. 157–161; Overall quality of evidence: Moderate).

PICO question 36: *Should we recommend IFX or ADA as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [23–29]. IFX (5 mg/kg IV q8w) was not more effective than ADA (40 mg SC eow) for maintenance of clinical remission (RR: 0.90, 95% CI: 0.55–1.49) and mucosal healing (RR: 1.05, 95% CI: 0.71–1.54) in adults with UC in remission. Moreover, we did not find any difference regarding AEs (RR: 1.01, 95% CI: 0.89–1.15) and SAEs (RR: 0.96, 95% CI: 0.61–1.54). (Appendix: pp. 162–163; Overall quality of evidence: Very low).

PICO question 37: *Should we recommend IFX or GLM as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [23–26, 30–32]. IFX (5 mg/kg IV q8w) was not more effective than GLM (100 mg SC q4w) for maintenance of clinical remission (RR: 0.66, 95% CI: 0.13–3.39) and mucosal healing (RR: 0.78, 95% CI: 0.32–1.89) in adults with UC in remission. Moreover, we did not find any difference regarding AEs (RR: 0.94, 95% CI: 0.78–1.13) and SAEs (RR: 1.15, 95% CI: 0.33–4.07). (Appendix: pp. 164–165; Overall quality of evidence: Very low).

PICO question 38: *Should we recommend ADA or GLM as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [27–32]. ADA (40 mg SC eow) was not more effective than GLM (100 mg SC q4w) for maintenance of clinical remission (RR: 0.73, 95% CI: 0.14–3.87) and mucosal healing (RR: 0.74, 95% CI: 0.30–1.85) in adults with UC in remission. Moreover, we did not find any difference regarding AEs (RR: 0.93, 95% CI: 0.75–1.15) and SAEs (RR: 1.20, 95% CI: 0.33–4.29). (Appendix: pp. 166–167; Overall quality of evidence: Very low).

PICO question 39: *Should we recommend IFX or VDZ as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [23–26,33–35]. IFX (5 mg/kg IV q8w) was not more effective than VDZ (300 mg IV q8w) for maintenance of clinical remission (RR: 0.84, 95% CI: 0.56–1.26) and mucosal healing (RR: 0.75, 95% CI: 0.52–1.07) in adults with UC in remission. Moreover, we did not find any difference regarding AEs (RR: 1.05, 95% CI: 0.94–1.17) and SAEs (RR: 1.15, 95% CI: 0.59–2.26). (Appendix: pp. 168–169; Overall quality of evidence: Very low).

PICO question 40: *Should we recommend IFX or UST as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [23–26,38]. IFX (5 mg/kg IV q8w) was not more effective than UST (90 mg SC q8w) for maintenance of clinical remission (RR: 1.09, 95% CI: 0.72–1.65) and mucosal healing (RR: 0.98, 95% CI: 0.68–1.41) in adults with UC in remission. Moreover, we did not find any difference regarding AEs (RR: 1.06, 95% CI: 0.96–1.18) and SAEs (RR: 1.22, 95% CI: 0.66–2.28). (Appendix: pp. 170–171; Overall quality of evidence: Very low).

PICO question 41: *Should we recommend IFX or TFB as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [23–26,36,37]. IFX (5 mg/kg IV q8w) was inferior to TFB (5 mg or 10 mg PO bid) for maintenance of clinical remission (RR: 0.59, 95% CI: 0.36–0.97) and mucosal healing (RR: 0.56, 95% CI: 0.36–0.87) in adults with UC in remission. We did not find any difference regarding AEs (RR: 1.07, 95% CI: 0.98–1.17) and SAEs (RR: 1.17, 95% CI: 0.69–1.99). (Appendix: pp. 172–173; Overall quality of evidence: Very low).

PICO question 42: *Should we recommend ADA or VDZ as maintenance treatment in adult patients with UC in remission?*
Evidence summary: Direct evidence from one RCT was used [39]. ADA (40 mg SC eow) was inferior to VDZ (300 mg IV q8w) for maintenance of clinical remission (RR: 0.72, 95% CI: 0.57–0.91; Figure 42a) and mucosal healing (RR: 0.70, 95% CI: 0.57–0.86; Figure 42b) in adults with UC in remission. There was not any difference regarding AEs (RR: 1.10, 95% CI: 1.00–1.22; Figure 42c) and SAEs (RR: 1.25, 95% CI: 0.86–1.83; Figure 42d). (Appendix: pp. 174–178; Overall quality of evidence: Moderate).

PICO question 43: *Should we recommend ADA or UST as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [27–29,38]. ADA (40 mg SC eow) was not more effective than UST (90 mg SC q8w) for maintenance of clinical remission (RR: 1.21, 95% CI: 0.71–2.05) and mucosal healing (RR: 0.94, 95% CI: 0.62–1.42) in adults with UC in remission. Moreover, we did not find any difference regarding AEs (RR: 1.05, 95% CI: 0.91–1.22) and SAEs (RR: 1.27, 95% CI: 0.66–2.45). (Appendix: pp. 179–180; Overall quality of evidence: Very low).

PICO question 44: *Should we recommend ADA or TFB as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [27–29,36,37]. ADA (40 mg SC eow) was inferior to TFB (5 mg or 10 mg PO bid) for maintenance of mucosal healing (RR: 0.53, 95% CI: 0.33–0.86) in adults with UC in remission; however, we did not find any difference regarding clinical remission (RR: 0.65, 95% CI: 0.36–1.18). Also, there was no difference concerning AEs (RR: 1.06, 95% CI: 0.92–1.22) and SAEs (RR: 1.21, 95% CI: 0.69–2.14). (Appendix: pp. 181–182; Overall quality of evidence: Very low).

PICO question 45: *Should we recommend GLM or VDZ as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [30–35]. We did not find any difference between GLM (100 mg SC q4w) and VDZ (300 mg IV q8w) for maintenance of clinical remission (RR: 1.27, 95% CI: 0.25–6.56) and mucosal healing (RR: 0.97, 95% CI: 0.39–2.38) in adults with UC in remission. Also, we found no difference in AEs (RR: 1.12, 95% CI: 0.92–1.37) and SAEs (RR: 1.00, 95% CI: 0.26–3.91). (Appendix: pp. 183–184; Overall quality of evidence: Very low).

PICO question 46: *Should we recommend GLM or UST as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [30–32,38]. We did not find any significant difference between GLM (100 mg

SC q4w) and UST (90 mg SC q8w) for maintenance of clinical remission (RR: 1.65, 95% CI: 0.32–8.55) and mucosal healing (RR: 1.27, 95% CI: 0.51–3.13) in adults with UC in remission. Also, we found no difference in AEs (RR: 1.13, 95% CI: 0.93–1.38) and SAEs (RR: 1.06, 95% CI: 0.28–4.05). (Appendix: pp. 185–186; Overall quality of evidence: Very low).

PICO question 47: *Should we recommend GLM or TFB as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [30–32,36,37]. We did not find any difference between GLM (100 mg SC q4w) and TFB (5 mg or 10 mg PO bid) for maintenance of clinical remission (RR: 0.89, 95% CI: 0.17–4.72) and mucosal healing (RR: 0.72, 95% CI: 0.28–1.84) in patients with UC in remission. Also, we found no difference in AEs (RR: 1.14, 95% CI: 0.94–1.38) and SAEs (RR: 1.01, 95% CI: 0.28–3.72). (Appendix: pp. 187–188; Overall quality of evidence: Very low).

PICO question 48: *Should we recommend VDZ or UST as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [33–35,38]. We did not find any difference between VDZ (300 mg IV q8w) and UST (90 mg SC q8w) for maintenance of clinical remission (RR: 1.30, 95% CI: 0.84–2.02) and mucosal healing (RR: 1.31, 95% CI: 0.89–1.93) in patients with UC in remission. Also, we found no difference in AEs (RR: 1.01, 95% CI: 0.89–1.15) and SAEs (RR: 1.06, 95% CI: 0.47–2.39). (Appendix: pp. 189–190; Overall quality of evidence: Very low).

PICO question 49: *Should we recommend VDZ or TFB as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [33–37]. We did not find any difference between VDZ (300 mg IV q8w) and TFB (5 mg or 10 mg PO bid) for maintenance of clinical remission (RR: 0.70, 95% CI: 0.42–1.18) and mucosal healing (RR: 0.74, 95% CI: 0.47–1.18) in adults with UC in remission. Also, we found no difference in AEs (RR: 1.02, 95% CI: 0.90–1.15) and SAEs (RR: 1.01, 95% CI: 0.48–2.14). (Appendix: pp. 191–192; Overall quality of evidence: Very low).

PICO question 50: *Should we recommend UST or TFB as maintenance treatment in adult patients with UC in remission?*
Evidence summary: An adjusted ITC was performed [36–38]. UST (90 mg SC q8w) was inferior to TFB (5 mg or 10 mg PO bid) for maintenance of clinical remission (RR: 0.54, 95% CI: 0.32–0.91) and mucosal healing (RR: 0.57, 95% CI: 0.36–0.90) in adult patients with UC in remission. There was no difference in AEs (RR: 1.01, 95% CI: 0.90–1.14) and SAEs (RR: 0.96, 95% CI: 0.47–1.93). (Appendix: pp. 193–194; Overall quality of evidence: Very low).

PICO question 51: *Should we recommend IFX plus immunosuppressant (AZA or MTX) or IFX monotherapy as maintenance treatment in adult patients with UC in remission?*
Evidence summary: Direct evidence from one RCT was used [44]. IFX plus immunosuppressant was not more effective than IFX monotherapy for maintenance of clinical remission (RR: 1.19, 95% CI: 0.87–1.62; Figure 51) in adult patients with UC in remission. (Appendix: pp. 195–196; Overall quality of evidence: Very low).

PICO question 52: *Should we recommend ADA plus immunosuppressant (AZA or MTX) or ADA monotherapy as maintenance treatment in adult patients with UC in remission?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 197).

PICO question 53: *Should we recommend GLM plus immunosuppressant (AZA or MTX) or GLM monotherapy as maintenance treatment in adult patients with UC in remission?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 198).

PICO question 54: *Should we recommend IFX plus immunosuppressant (AZA or MTX) or immunosuppressant monotherapy as maintenance treatment in adult patients with UC in remission?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 199).

PICO question 55: *Should we recommend ADA plus immunosuppressant (AZA or MTX) or immunosuppressant monotherapy as maintenance treatment in adult patients with UC in remission?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 200).

PICO question 56: *Should we recommend GLM plus immunosuppressant (AZA or MTX) or immunosuppressant monotherapy as maintenance treatment in adult patients with UC in remission?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 201).

PICO question 57: *Should we recommend therapeutic drug monitoring (TDM) or standard symptom-based approach of dose optimization in adult patients with UC having lost response to anti-TNF?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 202).

PICO question 58: *Should we recommend anti-TNF agent plus immunosuppressant or a therapeutic change in adult patients with UC having lost response to anti-TNFs despite dose-escalation?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 203).

PICO question 59: *Should we recommend withdrawal of anti-TNF treatment in adult patients with UC having achieved long-term deep remission?*
Evidence summary: Direct evidence from one RCT was considered [45]. Maintenance of clinical remission was significantly less common in patients who discontinued anti-TNF treatment (i.e. IFX) than in those who continued (RR: 0.68, 95% CI: 0.50–0.91; Figure 59a) in adults with UC in long-term deep remission. There was no difference regarding the occurrence of AEs (RR: 0.77, 95% CI: 0.29–2.04; Figure 59b). (Appendix: pp. 204–207; Overall quality of evidence: Very low).

PICO question 60: *Should we recommend UST in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: Direct evidence from RCTs was synthesized [38]. UST (6 mg/kg IV) was superior to placebo for induction of clinical remission (RR: 1.85, 95% CI: 1.03–3.33; Figure 60a), clinical response (RR: 1.86, 95% CI: 1.46–2.38; Figure 60b) and mucosal healing (RR: 1.57, 95% CI: 1.07–2.31; Figure 60c) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic drug. The occurrence of AEs (RR: 1.00, 95% CI: 0.92–1.10; Figure 60d) and SAEs (RR: 0.67, 95% CI: 0.39–1.17; Figure 60e) did not differ. (Appendix: pp. 208–213; Overall quality of evidence: Low).
PICO question 61: *Should we recommend IFX or UST in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*

Evidence summary: An adjusted ITC was performed [23–26,38]. We did not find any difference between IFX (5 mg/kg IV) and UST (6 mg/kg IV) regarding 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) in moderately-to-severely active UC naïve to any biologic agent. (Appendix: pp. 214–215; Overall quality of evidence: Very low).

PICO question 62: *Should we recommend ADA or UST in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [27–29,38]. ADA (160/80/40 mg SC) was inferior to UST (6 mg/kg IV) for induction of clinical response (RR: 0.74, 95% CI: 0.56–0.98) in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. We did not find any difference regarding clinical remission (RR: 0.94, 95% CI: 0.46–1.91), mucosal healing (RR: 0.85, 95% CI: 0.56–1.29), AEs (RR: 1.05, 95% CI: 0.91–1.22) and SAEs (RR: 1.27, 95% CI: 0.66–2.45). (Appendix: pp. 216–217; Overall quality of evidence: Very low).

PICO question 63: *Should we recommend GLM or UST in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [30–32,38]. We did not find any significant difference between GLM (200/100 mg SC) and UST (6 mg/kg IV) for induction of clinical remission (RR: 1.33, 95% CI: 0.63–2.80), clinical response (RR: 0.81, 95% CI: 0.57–1.14) and mucosal healing (RR: 0.90, 95% CI: 0.58–1.40) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic. Also, we found no difference in AEs (RR: 1.13, 95% CI: 0.93–1.38) and SAEs (RR: 1.06, 95% CI: 0.28–4.06). (Appendix: pp. 218–219; Overall quality of evidence: Very low).

PICO question 64: *Should we recommend VDZ or UST in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [33–35,38]. We did not find any difference between VDZ (300 mg IV) and UST (6 mg/kg IV) for induction of clinical remission (RR: 1.36, 95% CI: 0.58–3.15), clinical response (RR: 0.94, 95% CI: 0.62–1.40) and mucosal healing (RR: 1.13, 95% CI: 0.68–1.87) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic drug. Also, we found no difference in AEs (RR: 1.01, 95% CI: 0.89–1.15) and SAEs (RR: 1.06, 95% CI: 0.47–2.39). (Appendix: pp. 220–221; Overall quality of evidence: Very low).

PICO question 65: *Should we recommend TFB or UST in adult patients with moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic?*
Evidence summary: An adjusted ITC was performed [36–38]. We did not find any difference between TFB (10 mg PO) and UST (6 mg/kg IV) for induction of clinical remission (RR: 1.11, 95% CI: 0.53–2.35), clinical response (RR: 0.81, 95% CI: 0.59–1.13) and mucosal healing (RR: 1.05, 95% CI: 0.61–1.78) in moderately-to-severely active UC refractory to conventional therapy and naïve to any biologic drug. Also, we found no difference in AEs (RR: 0.99, 95% CI: 0.88–1.11) and SAEs (RR: 1.05, 95% CI: 0.52–2.11). (Appendix: pp. 222–223; Overall quality of evidence: Very low).

PICO question 66: *Should we recommend IFX or VDZ in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 224).

PICO question 67: *Should we recommend ADA or VDZ in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: Direct evidence from one RCT was considered [39]. ADA (160/80/40 mg SC) was inferior to VDZ (300 mg IV) for induction of clinical response (RR: 0.58, 95% CI: 0.40–0.84; Figure 67b) in moderately-to-severely active UC refractory to at least one biologic drug. However, there was not any significant difference regarding clinical remission (RR: 0.54, 95% CI: 0.27–1.10; Figure 67a), AEs (RR: 1.10, 95% CI: 1.00–1.22; Figure 67c) and SAEs (RR: 1.25, 95% CI: 0.86–1.83; Figure 67d). Also, using an adjusted ITC approach [27–29,33,34], we did not find any difference regarding mucosal healing (RR: 0.93, 95% CI: 0.47–1.84). (Appendix: pp. 225–229; Overall quality of evidence: Very low).

PICO question 68: *Should we recommend GLM or VDZ in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 230).

PICO question 69: *Should we recommend IFX or TFB in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 231).

PICO question 70: *Should we recommend ADA or TFB in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: An adjusted ITC was performed [27–29,36,37]. ADA (160/80/40 mg SC) was inferior to TFB (10 mg PO) for induction of clinical remission (RR: 0.16, 95% CI: 0.03–0.91) and mucosal healing (RR: 0.31, 95% CI: 0.14–0.71) in moderately-to-severely active UC refractory to at least one biologic. However, we did not find any significant difference for clinical response (RR: 0.61, 95% CI: 0.37–1.01), AEs (RR: 1.06, 95% CI: 0.92–1.22) and SAEs (RR: 1.21, 95% CI: 0.69–2.14). (Appendix: pp. 232–233; Overall quality of evidence: Very low).

PICO question 71: *Should we recommend GLM or TFB in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 234).

PICO question 72: *Should we recommend IFX or UST in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 235).

PICO question 73: *Should we recommend ADA or UST in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: An adjusted ITC was performed [27–29,38]. ADA (160/80/40 mg SC) was inferior to UST (6 mg/kg IV) for induction of clinical remission (RR: 0.13, 95% CI: 0.02–0.73), clinical response (RR: 0.61, 95% CI: 0.38–1.00) and mucosal healing (RR: 0.35, 95% CI: 0.16–0.76) in moderately-to-severely active UC refractory to at least one biologic agent. We did not find any significant difference for AEs (RR: 1.05, 95% CI: 0.91–1.22) and SAEs (RR: 1.27,

95% CI: 0.66–2.45). (Appendix: pp. 236–237; Overall quality of evidence: Very low).

PICO question 74: *Should we recommend GLM or UST in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
There was insufficient evidence to inform this clinical question. (Appendix: p. 238).

PICO question 75: *Should we recommend TFB or UST in adult patients with moderately-to-severely active UC refractory to at least one biologic?*
Evidence summary: An adjusted ITC was performed [36–38]. We did not find any difference between TFB (10 mg PO) and UST (6 mg/kg IV) for induction of clinical remission (RR: 0.83, 95% CI: 0.11–6.43), clinical response (RR: 1.01, 95% CI: 0.66–1.54) and mucosal healing (RR: 1.11, 95% CI: 0.43–2.85) in moderately-to-severely active UC refractory to at least one biologic drug. Also, we found no difference regarding the occurrence of AEs (RR: 0.99, 95% CI: 0.88–1.11) and SAEs (RR: 1.05, 95% CI: 0.52–2.11). (Appendix: pp. 239–240; Overall quality of evidence: Very low).

4. Discussion

The accumulating knowledge on the biologic mechanisms underlying UC has triggered an advance in drug development, drastically changing the therapeutic landscape. Biologics and small-molecule drugs have emerged, and frequently pose clinical dilemmas: physicians need to know how these therapies can be used to optimize patient outcomes.

Adhering to the GRADE methodology [11], this technical review systematically searched and identified the evidence to inform 75 PICO questions, synthesized it using rigorous meta-analytic methodology, appraised its quality, and concisely presented it in a transparent way, forming the basis for developing clinical recommendations on the use of biologics and small-molecule drugs in adult patients with UC. We are confident that we have used the totality of randomized evidence because we performed an extensive and rigorous search of three large biomedical databases; conducted supplemental searches in ClinicalTrials.gov to ensure identification of all eligible studies; and asked field experts from IG-IBD to check and provide additional evidences.

In summary, all the drugs (IFX, ADA, GLM, VDZ, UST, and TFB) were effective for induction of remission in biologic-naïve adults with moderately-to-severely active UC. However, ADA was inferior to IFX (regarding clinical response and mucosal healing), VDZ (clinical response) and UST (clinical response); and GLM was inferior to IFX (mucosal healing). In biologic-experienced patients with moderately-to-severely active UC, we found evidence of effectiveness only for UST and TFB (versus no treatment). Comparison among drugs showed UST being more effective than ADA (clinical remission, clinical response, mucosal healing) and VDZ (clinical remission and mucosal healing); TFB was more effective than ADA (clinical remission and mucosal healing) and VDZ (mucosal healing); and VDZ was more effective than ADA (clinical response). Among anti-TNF-based combination therapies, randomized evidence currently exists only for IFX combination with immunosuppressants being better than IFX monotherapy for induction of remission. For maintenance of remission, all the drugs (except GLM) were effective. However, TFB was superior to IFX (clinical remission and mucosal healing), UST (clinical remission and mucosal healing), and ADA (mucosal healing); and VDZ was superior to ADA (clinical remission and mucosal healing). Importantly, there is recent evidence that maintenance of remission in patients having achieved long-term deep remission is more common in those who continue anti-TNF (IFX) than in those who discontinue.

About one third of clinical questions (n = 23; 31%) were informed by direct, head-to-head comparisons offering evidence of varying quality, i.e. from high (n = 3), moderate (n = 8), low (n = 8), to very low (n = 4). However, a large number of clinical questions (n = 33; 44%) were informed by indirect evidence that was judged as of very low quality. This is due to the fact that, besides the VARSITY trial [39], head-to-head trials comparing biologics and small-molecule drugs are entirely missing in the field of UC [46–49]. Such studies (comparing IFX, ADA, GLM, VDZ, UST, and TFB, with each other) should be a top priority. Most importantly, several clinical questions (n = 19; 25%) could not be informed by high-quality data. This fact highlights knowledge gaps in several key areas that warrant further investigation to inform everyday clinical practice.

Future studies should not be designed solely with the aim of achieving drug marketing authorization. They should also aim to inform clinical practice, and clarify the position of the drugs in the existing therapeutic landscape of UC. Academia, pharmaceutical industry, relevant competent authorities and patient advocacy groups must collaborate in setting the research agenda.

Conflict of interest

Fabio Macaluso has served as an advisory board member and/or received lecture grants from AbbVie, Biogen, Galapagos, Janssen, MSD, Pfizer, Samsung Bioepis, and Takeda Pharmaceuticals. Ambrogio Orlando has 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. Stefano Festa has served as an advisory board member for Janssen Cilag, and received consultancy fees and/or educational grants from Takeda, SoFar, Abbvie, and Zambon. Claudio Papi has received consultancy fees and/or educational grants from Abbvie, MSD, Takeda, Pfizer, Janssen-Cilag, Sandoz, Chiesi, Sofar, Ferring and Zambon. Daniela Pugliese has received consultancy fees from Takeda, Jannsen-Cilag, Pfizer, and MSD. Alessandro Armuzzi has received 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, Roche, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mitsubishi Tanabe, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Tigenix, and research grants from MSD, Pfizer, Takeda. Stefanos Bonovas, Claudia Pansieri and Daniele Piovani have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.01.123.

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