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Guidelines

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

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ABSTRACT

The therapeutic armamentarium for the management of Crohn's disease (CD) is rapidly expanding. Several biologic therapies (e.g. infliximab, adalimumab, vedolizumab, and ustekinumab) have been regulatory approved, and there is considerable practice variability in the treatment of patients with CD.

This technical review systematically searched and identified the current evidence, synthesized it using meta-analytic methodology, appraised its quality, and concisely presented it, thus forming the basis for developing clinical practice recommendations on the use of biologic treatments in adult patients with CD.

1. Introduction

Crohn's disease (CD) is a chronic, progressive and destructive disorder of the gastrointestinal tract, characterized by transmural inflammation, a discontinuous pattern of distribution, a tendency to form strictures and fistulas, and periods of symptomatic disease alternating with periods of remission [1]. Typically, it involves distal ileum, ileocaecal region, colon and the perianal region, but it can affect any part of the digestive tract [1]. The etiology of CD remains uncertain, but clearly involves an interplay between genetic and environmental factors 2,3. The majority of patients complain of abdominal pain, diarrhea and weight loss, while many develop intestinal and extra-intestinal complications [4].

The armamentarium for the clinical management of CD has significantly expanded in the last years 5,6. Medical treatments include locally-acting steroids (such as budesonide), systemic steroids, thiopurines (azathioprine and mercaptopurine), methotrexate, and multiple biologic agents such as infliximab (IFX), adalimumab (ADA), vedolizumab (VDZ), and ustekinumab (UST). Such therapies aim for a deep and long-lasting remission, with the ultimate goal of preventing complications and halting the progressive course of the disease [7]. Notably, due to the availability of several therapeutic alternatives, there is considerable practice variability among providers caring for CD patients. This technical review synthesizes the current evidence, appraises its quality, and forms the evidence base for clinical practice recommendations on the use of biologic therapies in CD.

2. Methods

2.1. Overview

This work conforms to the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) methodology 8,9. We followed a stepwise process, which included: (i) formulation of clinical questions; (ii) identification of patient-important outcomes (i.e. outcomes that are important or critical for decision making); (iii) systematic review of the literature; (iv) evidence synthesis for each outcome across studies; and (v) grading of the quality of evidence for each outcome, followed by determining the overall quality of evidence across outcomes.

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2.2. Formulation of clinical questions

We formed 50 clinical questions using the PICO system that frames a health care question by defining: Population (P), Intervention (I), Comparator (C), and Outcomes (O). (Appendix: List of PICO questions, pp. 7–13).

2.3. Outcomes of interest

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

The panelists' agreement on outcomes' importance was assessed using the Disagreement Index (DI), as described in the RAND/UCLA appropriateness method [10]. A high DI value indicates wide 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.

2.4. Literature search and study selection

A systematic search of PubMed, Embase and Scopus databases was initially conducted in January 2020 –and was regularly updated through December 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 obtain a unique set of records. Two reviewers independently examined the search results, and screened titles and abstracts to exclude any clearly irrelevant articles. The full-text of selected publications was assessed for relevance, and reference lists were screened to identify further articles. Whenever pertinent data on study characteristics or outcomes were missing or unclearly presented in the original publications, we also searched the ClinicalTrials.gov website.

The totality of evidence informing the clinical questions derived from randomized, placebo-controlled or head-to-head trials involving adult patients with CD.

2.5. Data abstraction and quality assessment of primary studies

Two reviewers independently extracted the following information from each RCT: 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 mode of administration, as well as the efficacy and safety outcome data. Different doses of a certain drug were treated as different interventions: we considered only data for dosage and administration as approved in the respective Summary of Product Characteristics.

Two reviewers independently assessed risk-of-bias (RoB) in included studies using the Cochrane Collaboration's tool [11], 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 studies 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 in data extraction or RoB assessment were discussed and resolved via consensus.

2.6. Data synthesis and statistical analysis

The risk ratio (RR) was used to assess treatment effects. Study-level RRs with 95% confidence intervals (CIs) were calculated in accordance with the intention-to-treat 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 [12].

To synthesize the body of evidence for direct comparisons, we constructed forest plots and calculated the summary effect estimates using random-effects models (i.e. DerSimonian and Laird approach) [13]. Between-study heterogeneity was assessed with Cochran's Q test [14] with a 0.10 level of significance, and the I-squared metric [15] with any values over 50% being suggestive of significant heterogeneity. Publication bias could be assessed using funnel plots, as well as the Begg's and Egger's tests 16,17, 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 assessed the conceptual homogeneity across trials (i.e. study designs, populations, and outcomes) and, then, employed the Bucher's method of adjusted indirect comparisons [18]. According to this 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 (AEs and SAEs), we pooled all randomized data from induction and maintenance trials, and for all participants (i.e. those with and those without previous exposure to biologics).

For analyses of direct comparisons, we used the R software [19]. 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) [20]. All p-values are two-tailed. For all tests (except for heterogeneity), a p-value lower 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 summary RR 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 8,9. For each PICO, we first rated the quality of evidence separately for each patient-important outcome, and then determined the overall quality of evidence across outcomes. The quality of evidence demonstrates the certainty in a 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 clinical recommendation 8,9.

To determine the quality of evidence for each outcome, we started with rating the direct evidence from RCTs as of high quality, and then assessed five factors that could lead to rating down the quality:

- Risk of bias, i.e. limitations in study design or execution. It was assessed with the Cochrane's tool [11] as described above.
- Inconsistency, i.e. unexplained heterogeneity in results. It was assessed with the Cochran's Q test [14] with a 0.10 significance level, and the I-squared metric [15] 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. a pairwise meta-analysis was not feasible), we first examined conceptual homogeneity across RCTs and, then, used the Bucher's method [18]. The quality of evidence coming from the adjusted ITC was downgraded by two levels for indirectness.
- Imprecision, that characterizes the evidence coming from studies with few patients 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 16,17, 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 for the particular PICO.

Our judgement, regarding the quality of evidence identified and synthesized for each PICO question, was detailed in the respective evidence tables.

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 include the list of outcomes (and their importance for decision-making); number of participants, number of studies synthesized, and length of follow-up; our judgement about each factor determining the quality of evidence (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 (baseline risk); the risk with intervention group (risk of outcome in treated patients); the meta-analytic effect estimate (RR); the anticipated absolute effects (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.

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. The panel also considered the extent of resource use associated with alternative treatment options [9].

3. Results

3.1. Classification of importance of outcomes

Clinical remission, clinical response, mucosal healing and serious adverse events (SAEs) were judged as critical outcomes across all PICO questions. Adverse events (AEs) were judged as important outcome, but not critical for decision making. In the setting of complex perianal disease, fistula healing/closure was considered critical; also, prevention of endoscopic postoperative recurrence was judged as critical. There was consensus among panelists (DI<1.0) for all the outcomes (Appendix: Classification of importance of outcomes, p. 14).

3.2. Evidence search and selection process

Overall, 10,657 unique citations were identified, 246 publications were retrieved for detailed evaluation and, finally, 97 systematic reviews/meta-analyses and 37 RCTs were considered relevant.

A summary of the evidence search and selection process is reported in the Appendix (pp. 15–31), including a flowchart (p. 16), the list of the articles considered relevant to our guidelines (pp. 17–23), and the list of publications excluded, with the reasons for exclusion (pp. 24–30). The search algorithms, for PubMed, Embase and Scopus, are also presented (p. 31).

Randomized data were extracted from 37 publications [21–57], synthesized, and presented in SoF tables (Appendix: pp. 32–189), forming the basis for the evidence summaries that are reported below.

Overall, 25 of 50 PICO questions (50%) were informed by direct, head-to-head comparisons, with the quality of the respective evidence judged as: high (n = 1), moderate (n = 9), low (n = 6), or very low (n = 9). Fifteen PICOs (30%) were informed by indirect evidence (it was judged as very low quality in all cases). For 10 PICOs, the evidence was insufficient: data to complete the SoF table were not available.

PICO question 01: *Should we recommend IFX in adult patients with CD refractory to conventional therapy and naïve to any biologic?*

Evidence summary: Direct evidence from RCTs was synthesized [21–24]. IFX (5 mg/kg IV) was superior to placebo for induction of clinical remission (RR: 1.95, 95% CI: 1.59–2.40; Figure 01a) and mucosal healing (RR: 2.66, 95% CI: 1.66–4.27; Figure 01c) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic. We did not find any significant difference regarding clinical response (RR: 2.14, 95% CI: 0.91–5.03; Figure 01b), AEs (RR: 1.01, 95% CI: 0.94–1.08; Figure 01d) and SAEs (RR: 0.77, 95% CI: 0.51–1.17; Figure 01e). (Appendix: pp. 32–37; Overall quality of evidence: Moderate).

PICO question 02: *Should we recommend ADA in adult patients with CD refractory to conventional therapy and naïve to any biologic?*

Evidence summary: Direct evidence from RCTs was synthesized [25–31]. ADA (160/80 mg SC) was superior to placebo for induction of clinical remission (RR: 3.60, 95% CI: 2.19–5.92; Figure 02a) and clinical response (RR: 2.13, 95% CI: 1.44–3.16; Figure 02b) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic. The occurrence of AEs was not different (RR: 0.97, 95% CI: 0.87–1.08; Figure 02c); however, the risk of SAEs was significantly lower with ADA (RR: 0.59, 95% CI: 0.40–0.86; Figure 02d). (Appendix: pp. 38–42; Overall quality of evidence: Moderate).

PICO question 03: *Should we recommend IFX in adult patients with CD refractory to a previous therapy with an anti-TNF agent?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 43).

PICO question 04: *Should we recommend ADA in adult patients with CD refractory to a previous therapy with an anti-TNF agent?*

Evidence summary: Direct evidence from RCTs was synthesized [25–31]. ADA (160/80 mg SC) was superior to placebo for induction of clinical remission (RR: 3.00, 95% CI: 1.65–5.42; Figure 04a) and clinical response (RR: 1.54, 95% CI: 1.20–1.97; Figure 04b) in moderately-to-severely active CD refractory to a previous therapy with an anti-TNF treatment. The occurrence of AEs was not different (RR: 0.97, 95% CI: 0.87–1.08; Figure 04c); however, the risk of SAEs was significantly lower with ADA (RR: 0.59, 95% CI: 0.40–0.86; Figure 04d). (Appendix: pp. 44–48; Overall quality of evidence: Moderate).

PICO question 05: *Should we recommend IFX or ADA in adult patients with CD refractory to conventional therapy and naïve to any biologic?*

Evidence summary: An adjusted ITC was performed [21–31]. IFX (5 mg/kg IV) was inferior to ADA (160/80 mg SC) for induction of clinical remission (RR: 0.54, 95% CI: 0.32–0.93) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic treatment. We did not find any significant difference for clinical response (RR: 1.01, 95% CI: 0.39–2.57), AEs (RR: 1.04, 95% CI: 0.92–1.18) and SAEs (RR: 1.31, 95% CI: 0.74–2.30). (Appendix: pp. 49–50; Overall quality of evidence: Very low).

PICO question 06: *Should we recommend IFX or ADA in adult patients with CD refractory to a previous therapy with an anti-TNF agent?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 51).

PICO question 07: *Should we recommend VDZ in adult patients with CD refractory to conventional therapy and naïve to any biologic?*

Evidence summary: Direct evidence from RCTs was synthesized [32–34]. VDZ (300 mg IV) was superior to placebo for induction of clinical remission (RR: 2.18, 95% CI: 1.29–3.69; Figure 07a) and clinical response (RR: 1.47, 95% CI: 1.07–2.03; Figure 07b) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic. The risk of AEs (RR: 1.01, 95% CI: 0.95–1.09; Figure 07c) and SAEs (RR: 1.04, 95% CI: 0.75–1.44; Figure 07d) did not differ. (Appendix: pp. 52–56; Overall quality of evidence: Moderate).

PICO question 08: *Should we recommend VDZ in adult patients with CD refractory to at least one biologic?*

Evidence summary: Direct evidence from RCTs was synthesized [32–34]. VDZ (300 mg IV) was superior to placebo for induction of clinical response (RR: 1.51, 95% CI: 1.01–2.25; Figure 08b) in moderately-to-severely active CD refractory to at least one biologic. We did not find any significant difference for clinical remission (RR: 1.25, 95% CI: 0.62–2.53; Figure 08a), AEs (RR: 1.01, 95% CI: 0.95–1.09; Figure 08c) and SAEs (RR: 1.04, 95% CI: 0.75–1.44; Figure 08d). (Appendix: pp. 57–61; Overall quality of evidence: Moderate).

PICO question 09: *Should we recommend UST in adult patients with CD refractory to conventional therapy and naïve to any biologic?*

Evidence summary: Direct evidence from RCTs was synthesized [35–37]. UST (6 mg/kg IV) was superior to placebo for induction of clinical remission (RR: 2.06, 95% CI: 1.49–2.84; Figure 09a) and clinical response (RR: 1.73, 95% CI: 1.30–2.29; Figure 09b) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic. We did not find any significant difference regarding mucosal healing (RR: 1.89, 95% CI: 0.64–5.56; Figure 09c), AEs (RR: 0.96, 95% CI: 0.90–1.02; Figure 09d) and SAEs (RR: 0.79, 95% CI: 0.56–1.11; Figure 09e). (Appendix: pp. 62–67; Overall quality of evidence: Very low).

PICO question 10: *Should we recommend UST in adult patients with CD refractory to at least one biologic?*

Evidence summary: Direct evidence from RCTs was synthesized [35–37]. UST (6 mg/kg IV) was superior to placebo for induction of clinical remission (RR: 2.29, 95% CI: 1.40–3.76; Figure 10a) and clinical response (RR: 1.77, 95% CI: 1.39–2.26; Figure 10b) in moderately-to-severely active CD refractory to at least one biologic. We did not find any significant difference for mucosal healing (RR: 4.24, 95% CI: 0.15–123.1; Figure 10c), AEs (RR: 0.96, 95% CI: 0.90–1.02; Figure 10d) and SAEs (RR: 0.79, 95% CI: 0.56–1.11; Figure 10e). (Appendix: pp. 68–73; Overall quality of evidence: Very low).

PICO question 11: *Should we recommend IFX or VDZ in adult patients with CD refractory to conventional therapy naïve to any biologic?*

Evidence summary: An adjusted ITC was performed 21–24,32–34. We did not find any significant difference between IFX (5 mg/kg IV) and VDZ (300 mg IV) for induction of clinical remission (RR: 0.89, 95% CI: 0.51–1.57) and clinical response (RR: 1.46, 95% CI: 0.58–3.63) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic treatment. Similarly, we did not find any difference regarding AEs (RR: 1.00, 95% CI: 0.91–1.10) and SAEs (RR: 0.74, 95% CI: 0.44–1.26). (Appendix: pp. 74–75; Overall quality of evidence: Very low).

PICO question 12: *Should we recommend IFX or UST in adult patients with CD refractory to conventional therapy naïve to any biologic?*

Evidence summary: An adjusted ITC was performed 21–24,35–37. We did not find any significant difference between IFX (5 mg/kg IV) and UST (6 mg/kg IV) for induction of clinical remission (RR: 0.95, 95% CI: 0.65–1.39), clinical response (RR: 1.24, 95% CI: 0.50–3.04) and mucosal healing (RR: 1.41, 95% CI: 0.43–4.58) in moderately-to-severely active CD naïve to any biologic. Similarly, we did not find any difference regarding AEs (RR: 1.05, 95% CI: 0.96–1.16) and SAEs (RR: 0.98, 95% CI: 0.57–1.67). (Appendix: pp. 76–77; Overall quality of evidence: Very low).

PICO question 13: *Should we recommend ADA or VDZ in adult patients with CD refractory to conventional therapy naïve to any biologic?*

Evidence summary: An adjusted ITC was performed [25–34]. We did not find any significant difference between ADA (160/80 mg SC) and VDZ (300 mg IV) for induction of clinical remission (RR: 1.65, 95% CI: 0.80–3.40) and clinical response (RR: 1.45, 95% CI: 0.87–2.41) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic treatment. Also, the risk of AEs did not differ (RR: 0.96, 95% CI: 0.85–1.09); however, the risk of SAEs was significantly lower with ADA (RR: 0.57, 95% CI: 0.34–0.94). (Appendix: pp. 78–79; Overall quality of evidence: Very low).

PICO question 14: *Should we recommend ADA or UST in adult patients with CD refractory to conventional therapy naïve to any biologic?*

Evidence summary: Direct evidence from one RCT was considered [38]. ADA (160/80/40 mg SC) and UST (6 mg IV at baseline, then 90 mg SC e8w) did not differ regarding induction of clinical remission (RR: 1.05, 95% CI: 0.89–1.24; Figure 14a) and clinical response (RR: 0.99, 95% CI: 0.87–1.11; Figure 14b), AEs (RR: 0.97, 95% CI: 0.88–1.08; Figure 14c) and SAEs (RR: 1.25, 95% CI: 0.77–2.03; Figure 14d) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic drug. (Appendix: pp. 80–84; Overall quality of evidence: Moderate).

PICO question 15: *Should we recommend VDZ or UST in adult patients with CD refractory to at least one biologic?*

Evidence summary: An adjusted ITC was performed [32–37]. We did not find any significant difference between VDZ (300 mg IV) and UST (6 mg/kg IV) regarding induction of clinical remission (RR: 0.55, 95% CI: 0.23–1.29) and clinical response (RR: 0.85, 95% CI: 0.53–1.36) in moderately-to-severely active CD refractory to at least one biologic. Similarly, the risk of AEs (RR: 1.05, 95%

CI: 0.96–1.16) and SAEs (RR: 1.32, 95% CI: 0.82–2.11) did not differ. (Appendix: pp. 85–86; Overall quality of evidence: Very low).

PICO question 16: *Should we recommend IFX plus immunosuppressant or IFX monotherapy in adult patients with CD refractory to conventional therapy?*

Evidence summary: Direct evidence from RCTs was synthesized 23,39. IFX plus immunosuppressant was superior to IFX monotherapy regarding induction of clinical remission (RR: 1.29, 95% CI: 1.01–1.64; Figure 16a), clinical response (RR: 1.24, 95% CI: 1.05–1.47; Figure 16b) and mucosal healing (RR: 1.46, 95% CI: 1.00–2.13; Figure 16c) in moderately-to-severely active CD refractory to conventional therapy. The occurrence of AEs was not different (RR: 1.01, 95% CI: 0.94–1.09; Figure 16d); however, the risk of SAEs was significantly lower among patients receiving IFX plus immunosuppressant (RR: 0.62, 95% CI: 0.40–0.96; Figure 16e). (Appendix: pp. 87–92; Overall quality of evidence: Moderate).

PICO question 17: *Should we recommend ADA plus immunosuppressant or ADA monotherapy in adult patients with CD refractory to conventional therapy?*

Evidence summary: Direct evidence from RCTs was synthesized 40,41. ADA plus immunosuppressant was superior to ADA monotherapy for induction of mucosal healing (RR: 1.32, 95% CI: 1.06–1.65; Figure 17c) in moderately-to-severely active CD refractory to conventional therapy. However, we did not find any significant difference regarding clinical remission (RR: 0.95, 95% CI: 0.78–1.15; Figure 17a), clinical response (RR: 0.93, 95% CI: 0.79–1.11; Figure 17b) and AEs (RR: 1.23, 95% CI: 0.80–1.89; Figure 17d). (Appendix: pp. 93–97; Overall quality of evidence: Very low).

PICO question 18: *Should we recommend IFX as maintenance treatment in adult patients with CD achieving remission with IFX?*

Evidence summary: Direct evidence from RCTs was synthesized 22–24,42. IFX (5 mg/kg IV q8w) was superior to placebo for maintenance of clinical remission (RR: 2.08, 95% CI: 1.19–3.61; Figure 18a) in patients with CD in remission. We did not find any significant difference regarding mucosal healing (RR: 6.36, 95% CI: 0.86–46.9; Figure 18b), AEs (RR: 1.01, 95% CI: 0.94–1.08; Figure 18c) and SAEs (RR: 0.77, 95% CI: 0.51–1.17; Figure 18d). (Appendix: pp. 98–102; Overall quality of evidence: Very low).

PICO question 19: *Should we recommend ADA as maintenance treatment in adult patients with CD achieving remission with ADA?*

Evidence summary: Direct evidence from RCTs was synthesized [25–31]. ADA (40 mg SC eow) was superior to placebo for maintenance of clinical remission (RR: 2.68, 95% CI: 1.88–3.83; Figure 19a) and mucosal healing (RR: 31.2, 95% CI: 1.93–505.7; Figure 19b) in patients with CD in remission. The occurrence of AEs was not different (RR: 0.97, 95% CI: 0.87–1.08; Figure 19c); however, the risk of SAEs was significantly lower with ADA (RR: 0.59, 95% CI: 0.40–0.86; Figure 19d). (Appendix: pp. 103–107; Overall quality of evidence: Low).

PICO question 20: *Should we recommend VDZ as maintenance treatment in adult patients with CD achieving remission with VDZ?*

Evidence summary: Direct evidence from RCTs was synthesized [32–34]. VDZ (300 mg IV q8w) was superior to placebo for maintenance of clinical remission (RR: 1.84, 95% CI: 1.30–2.61; Figure 20a) in patients with CD in remission. The occurrence of AEs (RR: 1.01, 95% CI: 0.95–1.09; Figure 20b) and SAEs (RR: 1.04, 95% CI: 0.75–1.44; Figure 20c) did not differ. (Appendix: pp. 108–111; Overall quality of evidence: High).

PICO question 21: *Should we recommend UST as maintenance treatment in adult patients with CD achieving remission with UST?*

Evidence summary: Direct evidence from RCTs was synthesized [35–37]. UST (90 mg SC q8w) was superior to placebo for maintenance of clinical remission (RR: 1.47, 95% CI: 1.16–1.88; Figure 21a) in patients with CD in remission. We did not find any significant difference regarding mucosal healing (RR: 4.14, 95% CI: 0.52–33.1; Figure 21b), AEs (RR: 0.96, 95% CI: 0.90–1.02; Figure 21c) and SAEs (RR: 0.79, 95% CI: 0.56–1.11; Figure 21d). (Appendix: pp. 112–116; Overall quality of evidence: Low).

PICO question 22: *Should we recommend IFX or ADA as maintenance treatment in adult patients with CD?*

Evidence summary: An adjusted ITC was performed 22–31,42. We did not find any significant difference between IFX (5 mg/kg IV q8w) and ADA (40 mg SC eow) regarding maintenance of clinical remission (RR: 0.78, 95% CI: 0.40–1.50) and mucosal healing (RR: 0.20, 95% CI: 0.01–6.27) in patients with CD in remission. Similarly, we did not find any difference for AEs (RR: 1.04, 95% CI: 0.92–1.18) and SAEs (RR: 1.31, 95% CI: 0.74–2.30). (Appendix: pp. 117–118; Overall quality of evidence: Very low).

PICO question 23: *Should we recommend IFX or VDZ as maintenance treatment in adult patients with CD?*

Evidence summary: An adjusted ITC was performed 22–24,32–34. We did not find any significant difference between IFX (5 mg/kg IV q8w) and VDZ (300 mg IV q8w) regarding maintenance of clinical remission (RR: 1.13, 95% CI: 0.59–2.18) in patients with CD in remission. Similarly, we did not find any difference regarding AEs (RR: 1.00, 95% CI: 0.91–1.10) and SAEs (RR: 0.74, 95% CI: 0.44–1.26). (Appendix: pp. 119–120; Overall quality of evidence: Very low).

PICO question 24: *Should we recommend IFX or UST as maintenance treatment in adult patients with CD?*

Evidence summary: An adjusted ITC was performed 22–24,35–37,42. We did not find any significant difference between IFX (5 mg/kg IV q8w) and UST (90 mg SC q8w) regarding maintenance of clinical remission (RR: 1.41, 95% CI: 0.77–2.59) and mucosal healing (RR: 1.54, 95% CI: 0.09–27.4) in patients with CD in remission. Similarly, we did not find any difference for AEs (RR: 1.05, 95% CI: 0.96–1.16) and SAEs (RR: 0.98, 95% CI: 0.57–1.67). (Appendix: pp. 121–122; Overall quality of evidence: Very low).

PICO question 25: *Should we recommend ADA or VDZ as maintenance treatment in adult patients with CD?*

Evidence summary: An adjusted ITC was performed [25–34]. We did not find any significant difference between ADA (40 mg SC eow) and VDZ (300 mg IV q8w) regarding maintenance of clinical remission (RR: 1.46, 95% CI: 0.89–2.40) in patients with CD in remission. Also, the risk of AEs was not different (RR: 0.96, 95% CI: 0.85–1.09); however, the risk of SAEs was significantly lower with ADA (RR: 0.57, 95% CI: 0.34–0.94). (Appendix: pp. 123–124; Overall quality of evidence: Very low).

PICO question 26: *Should we recommend ADA or UST as maintenance treatment in adult patients with CD?*

Evidence summary: Direct evidence from one RCT was considered [38]. ADA (40 mg SC eow) and UST (90 mg SC q8w) did not differ for maintenance of clinical remission (RR: 0.94, 95% CI: 0.81–1.10; Figure 26a) and mucosal healing (RR: 1.08, 95% CI: 0.78–1.48; Figure 26b) in patients with CD in remission. Similarly, the occurrence of AEs (RR: 0.97, 95% CI: 0.88–1.08; Figure 26c) and SAEs (RR: 1.25, 95% CI: 0.77–2.03; Figure 26d) did not differ. (Appendix: pp. 125–129; Overall quality of evidence: Moderate).

PICO question 27: *Should we recommend VDZ or UST as maintenance treatment in adult patients with CD?*

Evidence summary: An adjusted ITC was performed 32–35,37. We did not find any significant difference between VDZ (300 mg IV q8w) and UST (90 mg SC q8w) regarding maintenance of clinical remission (RR: 1.25, 95% CI: 0.82–1.91) in patients with CD in remission. Similarly, the risk of AEs (RR: 1.05, 95% CI: 0.96–1.16) and SAEs (RR: 1.32, 95% CI: 0.82–2.11) did not differ. (Appendix: pp. 130–131; Overall quality of evidence: Very low).

PICO question 28: *Should we recommend IFX plus immunosuppressant or IFX monotherapy as maintenance treatment in adults with CD achieving remission with IFX plus immunosuppressant?*

Evidence summary: Direct evidence from one RCT was considered [43]. IFX plus immunosuppressant was not more effective

than IFX monotherapy for maintenance of clinical remission (RR: 0.89, 95% CI: 0.53–1.48; Figure 28a) and mucosal healing (RR: 1.14, 95% CI: 0.65–2.02; Figure 28b) in patients with CD having achieved remission with IFX plus immunosuppressant. Similarly, the occurrence of AEs (RR: 0.96, 95% CI: 0.68–1.36; Figure 28c) and SAEs (RR: 1.00, 95% CI: 0.21–4.66; Figure 28d) did not differ. (Appendix: pp. 132–136; Overall quality of evidence: Very low).

PICO question 29: *Should we recommend ADA plus immunosuppressant or ADA monotherapy as maintenance treatment in adults with CD achieving remission with ADA plus immunosuppressant?*

Evidence summary: Direct evidence from one RCT was considered [44]. ADA plus immunosuppressant was not more effective than ADA monotherapy for maintenance of clinical remission (RR: 1.03, 95% CI: 0.90–1.18; Figure 29a) and mucosal healing (RR: 0.95, 95% CI: 0.39–2.35; Figure 29b) in patients with CD having achieved remission with ADA plus immunosuppressant. Similarly, the occurrence of AEs (RR: 0.32, 95% CI: 0.04–2.65; Figure 29c) did not significantly differ. (Appendix: pp. 137–141; Overall quality of evidence: Very low).

PICO question 30: *Should we recommend IFX plus immunosuppressant or immunosuppressant monotherapy as maintenance treatment in adult patients with CD achieving remission with IFX plus immunosuppressant?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 142).

PICO question 31: *Should we recommend ADA plus immunosuppressant or immunosuppressant monotherapy as maintenance treatment in adult patients with CD achieving remission with ADA plus immunosuppressant?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 143).

PICO question 32: *Should we recommend therapeutic drug monitoring (TDM) or a standard symptom-based approach of dose optimization in adult patients with CD having lost response to anti-TNF agents?*

Evidence summary: Direct evidence from one RCT was considered [45]. "Therapeutic drug monitoring" and the "standard symptom-based approach of dose optimization" had comparable efficacy in terms of recapturing clinical remission (RR: 0.78, 95% CI: 0.40–1.51; Figure 32a) and clinical response (RR: 1.09, 95% CI: 0.71–1.67; Figure 32b) in patients with CD having lost response to an anti-TNF treatment. (Appendix: pp. 144–146; Overall quality of evidence: Very low).

PICO question 33: *Should we recommend anti-TNF agent plus immunosuppressant or a therapeutic change in adult patients with CD having lost response to anti-TNFs despite dose-escalation?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 147).

PICO question 34: *Should we recommend withdrawal or continuation of anti-TNF treatment in adult patients with CD having achieved long-term deep remission?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 148).

PICO question 35: *Should we recommend IFX in adult patients with complex perianal CD?*

Evidence summary: Direct evidence from RCTs was synthesized 46,47. IFX (5 mg/kg IV at wks 0, 2, 6; and q8w thereafter) was superior to placebo for achievement (RR: 4.25, 95% CI: 1.61–11.20; Figure 35a) and maintenance of fistula healing/closure (RR: 1.79, 95% CI: 1.10–2.92; Figure 35b) in patients with complex perianal CD. The occurrence of AEs (RR: 0.97, 95% CI: 0.90–1.04; Figure 35c) and SAEs (RR: 0.63, 95% CI: 0.38–1.04; Figure 35d) did not significantly differ. (Appendix: pp. 149–153; Overall quality of evidence: Low).

PICO question 36: *Should we recommend ADA in adult patients with complex perianal CD?*

Evidence summary: Direct evidence from RCTs was synthesized 26,27,30. ADA (160 mg SC at wk 0; 80 mg at wk 2; and then 40 mg eow) was not better than placebo for achieving fistula healing/closure in the short term (RR: 0.43, 95% CI: 0.07–2.55; Figure 36a) in patients with complex perianal CD; however, ADA was significantly more efficacious in the long term (RR: 2.87, 95% CI: 1.19–6.95; Figure 36b). (Appendix: pp. 154–156; Overall quality of evidence: Low).

PICO question 37: *Should we recommend IFX or ADA in adult patients with complex perianal CD?*

Evidence summary: An adjusted ITC was performed 26,27,30,46,47. IFX (5 mg/kg IV at wks 0, 2, 6; and q8w thereafter) was superior to ADA (160 mg SC at wk 0; 80 mg at wk 2; and then 40 mg eow) for achieving fistula healing/closure in the short term (RR: 9.88, 95% CI: 1.28–76.2) in complex perianal CD; however, IFX and ADA did not significantly differ in the long term (RR: 0.62, 95% CI: 0.23–1.71). (Appendix: pp. 157–158; Overall quality of evidence: Very low).

PICO question 38: *Should we recommend VDZ in adult patients with complex perianal CD?*

Evidence summary: Direct evidence from one RCT was considered [48]. VDZ (300 mg IV) was not significantly better than placebo for achieving fistula healing/closure (RR: 2.23, 95% CI: 0.57–8.72; Figure 38) in complex perianal CD. (Appendix: pp. 159–160; Overall quality of evidence: Very low).

PICO question 39: *Should we recommend UST in adult patients with complex perianal CD?*

Evidence summary: Direct evidence from RCTs was considered [49]. UST (6 mg/kg IV) was not significantly better than placebo for achieving fistula healing/closure (RR: 1.98, 95% CI: 0.98–4.00; Figure 39) in complex perianal CD. (Appendix: pp. 161–162; Overall quality of evidence: Low).

PICO question 40: *Should we recommend stem cells-based therapy in adult patients with complex perianal CD?*

Evidence summary: Direct evidence from one RCT was considered 50,51. Stem cells-based therapy (allogeneic expanded adipose-derived mesenchymal stem cells) was not significantly better than placebo for achieving fistula healing/closure at 24 weeks (RR: 1.30, 95% CI: 0.97–1.74; Figure 40a) in patients with complex perianal CD; however, it was significantly more efficacious at 52 weeks (RR: 1.43, 95% CI: 1.07–1.90; Figure 40b). The occurrence of AEs (RR: 1.06, 95% CI: 0.90–1.24; Figure 40c) and SAEs (RR: 1.18, 95% CI: 0.71–1.97; Figure 40d) did not differ. (Appendix: pp. 163–167; Overall quality of evidence: Low).

PICO question 41: *Should we recommend IFX in adult patients with CD at high risk for post-operative recurrence?*

Evidence summary: Direct evidence from RCTs was synthesized [52–56]. IFX (5 mg/kg IV at wks 0, 2, 6; and q8w thereafter) was superior to placebo for prevention of endoscopic postoperative recurrence (RR: 3.44, 95% CI: 1.36–8.71; Figure 41b) in patients with CD at high risk for post-operative recurrence. We did not find any significant difference regarding maintenance of clinical remission (RR: 1.24, 95% CI: 0.90–1.71; Figure 41a). Also, the risk of AEs (RR: 1.15, 95% CI: 0.72–1.84; Figure 41c) and SAEs (RR: 0.87, 95% CI: 0.56–1.35; Figure 41d) did not differ. (Appendix: pp. 168–172; Overall quality of evidence: Moderate).

PICO question 42: *Should we recommend ADA in adult patients with CD at high risk for post-operative recurrence?*

Evidence summary: An adjusted ITC was performed 52,54–57. ADA (160 mg SC at wk 0; 80 mg at wk 2; and then 40 mg eow) was superior to placebo for prevention of endoscopic postoperative recurrence (RR: 3.87, 95% CI: 1.42–10.5) in patients with CD at high risk for post-operative recurrence; however, we did not find any significant difference for the maintenance of clinical remission (RR: 1.24, 95% CI: 0.80–1.91). (Appendix: pp. 173–174; Overall quality of evidence: Very low).

PICO question 43: *Should we recommend IFX or ADA in adult patients with CD at high risk for post-operative recurrence?*

Evidence summary: Direct evidence from one RCT was considered [57]. IFX (5 mg/kg IV at wks 0, 2, 6; and q8w thereafter) and ADA (160 mg SC at wk 0; 80 mg at wk 2; and then 40 mg eow) did not differ regarding maintenance of clinical (RR: 1.00, 95% CI: 0.75–1.34; Figure 43a) and endoscopic remission (RR: 0.89, 95% CI: 0.61–1.29; Figure 43b) in patients with CD at high risk for post-operative recurrence. (Appendix: pp. 175–179; Overall quality of evidence: Very low).

PICO question 44: *Should we recommend VDZ in adult patients with CD at high risk for post-operative recurrence?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 180).

PICO question 45: *Should we recommend UST in adult patients with CD at high risk for post-operative recurrence?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 181).

PICO question 46: *Should we recommend VDZ or UST in adult patients with CD refractory to conventional therapy and naïve to any biologic?*

Evidence summary: An adjusted ITC was performed [32–37]. We did not find any difference between VDZ (300 mg IV) and UST (6 mg/kg IV) for induction of clinical remission (RR: 1.06, 95% CI: 0.57–1.96) and clinical response (RR: 0.85, 95% CI: 0.55–1.30) in moderately-to-severely active CD refractory to conventional therapy and naïve to any biologic treatment. Similarly, we did not find any difference for AEs (RR: 1.05, 95% CI: 0.96–1.16) and SAEs (RR: 1.32, 95% CI: 0.82–2.11). (Appendix: pp. 182–183; Overall quality of evidence: Very low).

PICO question 47: *Should we recommend IFX or VDZ in adult patients with CD refractory to conventional therapy and to at least one biologic?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 184).

PICO question 48: *Should we recommend IFX or UST in adult patients with CD refractory to conventional therapy and to at least one biologic?*

There was insufficient evidence to inform this clinical question. (Appendix: p. 185).

PICO question 49: *Should we recommend ADA or VDZ in adult patients with CD refractory to conventional therapy and to at least one biologic?*

Evidence summary: An adjusted ITC was performed [25–34]. We did not find any significant difference between ADA (160/80 mg SC) and VDZ (300 mg IV) for induction of clinical remission (RR: 2.40, 95% CI: 0.96–6.03) and clinical response (RR: 1.02, 95% CI: 0.64–1.63) in moderately-to-severely active CD refractory to conventional therapy and to at least one biologic treatment. Also, the risk of AEs did not differ (RR: 0.96, 95% CI: 0.85–1.09); however, the risk of SAEs was significantly lower with ADA (RR: 0.57, 95% CI: 0.34–0.94). (Appendix: pp. 186–187; Overall quality of evidence: Very low).

PICO question 50: *Should we recommend ADA or UST in adult patients with CD refractory to conventional therapy and to at least one biologic?*

Evidence summary: An adjusted ITC was performed 25–31,35,37. We did not find any significant difference between ADA (160/80 mg SC) and UST (6 mg/kg IV) regarding induction of clinical remission (RR: 1.31, 95% CI: 0.61–2.84) and clinical response (RR: 0.87, 95% CI: 0.62–1.23), AEs (RR: 1.01, 95% CI: 0.89–1.15) and SAEs (RR: 0.75, 95% CI: 0.45–1.25) in moderately-to-severely active CD refractory to conventional therapy and to at least one biologic treatment. (Appendix: pp. 188–189; Overall quality of evidence: Very low).

4. Discussion

This technical review systematically searched and identified evidence to inform 50 clinical questions, synthesized it with rigorous meta-analytic methodology, appraised its quality, and concisely presented it in a transparent manner, forming the basis for developing clinical practice recommendations on the use of biologic treatments in adult patients with CD. Having conducted an extensive literature search (i.e. investigation of three large biomedical databases: PubMed, Embase and Scopus; and supplemental searches in ClinicalTrials.gov), and having involved field experts from the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) to check and provide additional references, we are confident that the totality of relevant randomized evidence has been considered in this work.

In summary, we found that all biologics (IFX, ADA, VDZ, UST) were effective for induction of remission in biologic-naïve patients with moderately-to-severely active CD. However, ADA was superior to IFX (for induction of clinical remission). All other comparisons between biologic drugs did not show evidence of different efficacy. In biologic-experienced patients, we found strong evidence of effectiveness for ADA, VDZ, and UST (versus placebo). None of the comparisons between biologic treatments showed evidence of superiority. Regarding anti-TNF-based combination therapies for induction of remission, IFX combination with immunosuppressants was superior to IFX monotherapy (for clinical remission, clinical response, and mucosal healing) and ADA combination with immunosuppressants was superior to ADA monotherapy (for mucosal healing). For maintenance of remission, all treatments (IFX, ADA, VDZ, UST) were effective (versus placebo), with none of the comparisons between biologics reaching statistical significance. In the setting of complex perianal disease, IFX was effective in achieving and maintaining fistula healing/closure, while ADA was effective only for maintenance of fistula healing/closure. Finally, for prophylaxis of post-operative recurrence, both IFX and ADA were effective for the prevention of endoscopic postoperative recurrence.

Half of the clinical questions ($n = 25$; 50%) were informed by direct, head-to-head clinical trials offering evidence of varying quality, i.e. from high ($n = 1$) and moderate ($n = 9$), to low ($n = 6$) and very low ($n = 9$). However, almost one third of the clinical questions ($n = 15$; 30%) were informed by indirect evidence judged as of very low quality. This was due to the fact that, besides the SEAVUE trial [38] and the small study by Tursi et al. [57], head-to-head trials comparing biologic drugs are lacking in the field of CD. Such studies –comparing IFX, ADA, VDZ, UST, with each other– should be high in the research agenda. Finally, several clinical questions ($n = 10$; 20%) could not be informed by high-quality randomized data. This highlights important knowledge gaps in key areas of everyday clinical practice.

Further studies (especially head-to-head trials and trials combining drugs targeting different pathways) are warranted to inform the evidence base and assist physicians through the decision-making process, investigating comparative effectiveness, long-term safety profiles, cost, and patient preferences.

Conflict of interest

Fabio Macaluso has served as an advisory board member and/or received lecture grants from AbbVie, Biogen, Ferring, Galapagos, Janssen, MSD, Pfizer, Samsung Bioepis, and Takeda. Ambrogio Orlando has served as an advisory board member for AbbVie, Galapagos, MSD, Janssen, Pfizer, Takeda, and received lecture fees from AbbVie, MSD, Sofar, Chiesi, Janssen, Pfizer, and Takeda. Stefano Festa has served as an advisory board member for Janssen Cilag, and received consultancy fees and/or educational grants from Takeda, SoFar, Abbvie, Pfizer, and Zambon. Claudio Papi has re-

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

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Supplementary materials

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