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ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:
Raine, T., Bonovas, S., Burisch, J., Kucharzik, T., Adamina, M., Annese, V., et al. (2022). ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. JOURNAL OF CROHN'S AND COLITIS, 16(1), 2-17 [10.1093/ecco-jcc/jjab178].

Availability:
This version is available at: https://hdl.handle.net/11585/873530 since: 2022-02-28

Published:

DOI: http://doi.org/10.1093/ecco-jcc/jjab178

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08 May 2026

Manuscript Doi: 10.1093/ecco-jcc/jjab178

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

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1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory bowel disease [IBD] characterised by colonic inflammation extending to a variable extent from the rectum. Care of the patient with UC requires appropriate input from across the multiprofessional team. These guidelines summarise the recommended medical treatment for adults with UC. Other ECCO guidelines consider the approach to UC diagnosis and monitoring,[1–3] nursing care,[4] management of disease complications,[5–7] risk of infection,[8] and technical aspects of surgery.[9] This document was prepared as part of a process that also led to the publication of a related guideline with recommendations on the surgical care of the patients with UC and on the medical aspects of the management of the patient hospitalised with severe UC.[Ed: insert crossref to surgical paper here]

Patients living with UC can have a variable disease course.[10] In this document, we discuss therapeutic approaches stratified by disease severity [mildly-to-moderately active and moderately-to-severely active disease]. Attempts to define disease severity are widely used in setting clinical trial inclusion criteria and can be measured according to several different definitions.[11] Trial populations will inevitably vary and we reflect the continuum of disease severity by having the moderate disease category span both broad categories. It is also important to remember that these definitions capture

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severity at a given point in time and may not reflect the cumulative long-term burden of disease experienced by a patient.[12]

It is also important to consider disease extent when planning treatment in UC, as this may affect the optimal route of drug administration. This is typically defined according to disease involving the rectum only [proctitis], disease distal to the splenic flexure [left-sided UC], or disease extending proximal to the splenic flexure [extensive UC].[13] These definitions of disease extent are recognised as somewhat arbitrary; in clinical practice, topically administered therapies are often used for UC whose extent is limited to the rectum and a portion of the sigmoid colon [proctosigmoiditis], with the term 'distal colitis' used to describe this disease distribution. It should be remembered that disease distribution can change[10,14] and that proximal disease extension can be a negative prognostic marker.[15]

2. Methods

This document was compiled following the 'Grading of Recommendations Assessment, Development, and Evaluation' [GRADE] methodology.[16] A panel of 33 experts was selected by the Guidelines Committee of ECCO from a competitive pool of applicants and worked with a team of methodologists and librarians. All panellists received training in the GRADE methodology. Additionally, 6 patients with UC representing the European Federation of Crohn's and Colitis Associations [EFCCA] were invited to participate in all face-to-face meetings as full voting members.

Two domains for the medical treatment of UC were identified and used as the basis for the following two working groups based upon disease severity: mildly-to-moderately active disease and moderately-to-severely active disease. We recognise that these divisions are somewhat arbitrary,

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partially overlapping, and inconsistently defined; therefore, we ensured close collaboration between the working groups to ensure that key topics were covered appropriately with the aim of providing guidance applicable across the continuum of UC severity encountered in clinical practice.

Working group participants first formulated a series of specific questions using the Population, Intervention, Comparator, Outcomes [PICO] system, which were deemed to be clinically important for the medical treatment of UC. These questions were debated in a series of telephone conferences prior to final agreement at a meeting of the full guideline group in Vienna in November 2019. Voting on the inclusion of PICO questions was conducted and only those achieving agreement of > 80% by the panel were included in the next phase of the process. At this meeting, the panellists also ranked each outcome's importance on a scale of 1 to 9 based on the GRADE definitions.[16] 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 panellists' agreement on outcomes' importance was assessed using the Disagreement Index, as described in the RAND/UCLA appropriateness method.[17]

The team of librarians performed a comprehensive literature search on PubMed/Medline, Embase, and the Cochrane Central databases using specific search strings for each PICO question [available as Supplementary data at ECCO-JCC online]. Two working group members [one assigned to the PICO question and another from the same group as second reviewer] independently screened titles and abstracts to exclude any irrelevant reports. Subsequently, the working group members assigned to each PICO question assessed the full text of the selected publications for relevance to the specific PICO. Note that studies were only selected if they addressed the PICO as formulated, including data on at least one of the outcomes of interest for the relevant dose of the intervention. In some instances, this meant that RCTs of a drug of interest were not included because, for example, they did not report at least one outcome defined as being of critical importance.

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Most of the evidence informing the guidelines in this document came from randomised controlled trials [RCT] conducted in adult patients with UC. The methodologists directly performed the comparisons. The risk ratio [RR] was used to measure treatment effects. Study-level RRs with 95% confidence intervals [CI] 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 other group. To synthesize the evidence, we prepared forest plots and calculated the pooled effect estimates using random-effects models [DerSimonian and Laird approach].[18] We used R software for statistical analysis. All *p*-values are two-tailed. For all tests [except for heterogeneity], a p-value < 0.05 indicates statistical significance.

To calculate absolute benefits and harms, we relied on the pooled event rates in the control groups. The absolute effect was based on the pooled RR and the baseline risk in the control groups.

The quality of evidence was expressed using the following four categories: high, moderate, low, and very low. For each PICO question, we rated the quality of evidence separately for each patient-important outcome, and then determined the overall quality of evidence across outcomes. 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.[16]

To determine the quality of the evidence for each outcome across all studies, we started with rating the evidence from RCTs as 'high' quality, and then assessed the following five factors that could lead to downrating the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[16] Risk of bias was assessed using the Cochrane tool. Inconsistency was assessed with the Cochrane Q test [using a 0.10 significance level] and the I^2 metric [with values > 50% suggesting significant heterogeneity]. Indirectness was determined according to whether the studies addressed a different but related population, intervention, or outcome from the one of interest.

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Imprecision was based on the number of events [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]. Publication bias was assessed using funnel plots, and the Begg's and Egger's tests only if there were at least 10 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. Summary-of-Findings [SoF] tables showing all studies used in preparing each recommendation, key data and study findings for each outcome of interest, and our judgements about each of the quality of evidence factors examined are available as Supplementary material, along with documentation of the assessment of evidence quality. We present our rating of quality of evidence for each one of the outcomes; the risk with control group; the risk with intervention group; the meta-analytic effect estimate; the anticipated absolute effects; and any other relevant information regarding the data reported in the SoF table, along with our rating of the overall quality of evidence across outcomes.

The strength of each recommendation was graded either as 'strong' [meaning that the desirable effects of an intervention clearly outweigh the undesirable effects, or vice versa] or as 'weak' [meaning that the balance is less certain] while also considering the quality of evidence, values and preferences of patients, balance between desirable and undesirable effects, and cost effectiveness. All recommendations were subject to online voting by the panel members, the ECCO National Representatives [two for each country affiliated with ECCO], six reviewers from the European Society of Coloproctology, and nine additional reviewers from a list of ECCO members involved in ECCO guideline development [see Acknowledgements section]. The final version of all

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statements/recommendations was discussed among panel members during a final virtual consensus meeting in April 2021 and put to a vote; final recommendations were approved if at least 80% of the panellists agreed with the statement and its associated strength grading. The list of statements, supporting text and material, and manuscript draft were critically reviewed by the ECCO Governing Board members, who also approved the final version of these Guidelines.

These guidelines are designed to inform and support clinicians in making evidence-based decisions on the medical treatment of UC; they should not be used to signify a minimal acceptable standard of care, should not be used for medicolegal purposes, and should not be interpreted as endorsing the use of any particular proprietary or commercial product. All costs associated with the development and publication of this guideline were met by ECCO. The Governing Board of ECCO played no role in the selection of panel members or the development or selection of PICO questions. A summary of some of the key changes from previous ECCO UC guidelines is presented in the Supplementary material.

3. General approach to the management of ulcerative colitis

These guidelines set out the evidence for the use of different medical therapies in the treatment of UC. They were developed and written in a manner driven by the available data, which were typically from large-scale clinical trials and usually based upon testing of an intervention against placebo. Nevertheless, the medical care of a patient with UC goes well beyond the selection between a given drug and no treatment. Furthermore, patients encountered in the clinic frequently do not fit the profile of a given clinical trial population. It is therefore important that these guidelines are used first to inform the physician of the quality of evidence behind any given treatment, which the physician must then consider, together with the patient, in formulating a treatment plan.

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A key area of debate is when to escalate treatment. There is less evidence in UC than in Crohn's disease on the importance of early treatment escalation. At the same time, the experience of recurrent symptom flares can lead to physical and psychological harm,[19,20] as can repeated exposure to corticosteroids.[21] Although the cost of an intervention is a factor reflected in the GRADE process when forming the strength of recommendation, as international guidelines there will be local health economic considerations that this document can not address. Nevertheless, it is clear that appropriate and timely selection of patients for higher-cost interventions is critical to achieve optimal health economic outcomes.[22,23]

The ultimate goal of treatment in UC is to maintain health-related quality of life [QoL] and avoid disability.[24] To achieve this, it is important to not only provide rapid relief of clinical symptoms, but also achieve endoscopic healing where possible, as this is associated with improved long-term outcomes.[25–27] The importance of these outcomes was reflected in the decision by the expert panel to select endoscopic and clinical outcomes as being of critical importance.

The term 'conventional therapy' has been widely used in the past to differentiate well established traditional treatments (such as 5-aminosalicylates [5-ASA], corticosteroids, and thiopurine immunomodulators) from biologic therapies and other novel targeted small molecules. This concept is becoming somewhat outdated, as the costs of and access to biologics therapies evolves [notably with the introduction of biosimilars] and biologics are increasing viewed as a conventional part of UC treatment. For the purposes of this guideline, we agreed to use the term 'conventional therapy' as it has traditionally been understood in the absence of any widely accepted alternative nomenclature, while also accepting the limitations of this language. Where specific definitions of conventional therapy have been used in individual studies, this is outlined in the supporting SOF tables.

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Dose escalation has been reported for many of the interventions we considered, typically in a non-randomised manner, both for patients showing disease flares during RCTs or in cohort studies. Although appropriate dose escalation or dose optimisation can play a role in clinical practice, there are minimal high-quality trial data in this area, and uncontrolled studies are subject to several potential forms of bias. For this reason, we have restricted our recommendations to the doses studied in a randomised manner in clinical trials. In addition to the initiation and escalation of medical treatments for UC, how and when to consider reducing or stopping treatment to minimise the risks, costs, and burden to patients of prolonged drug therapy is an important consideration. The limited evidence on treatment withdrawal has been reviewed recently and is beyond the scope of this current guideline.[28]

4. Medical management of mildly-to-moderately active ulcerative colitis

4.1: Induction of remission in mildly-to-moderately active ulcerative colitis

5-Aminosalicylates

Recommendation 1

We recommend 5-aminosalicylates at a dose of ≥ 2 g/d to induce remission in patients with mildly-to-moderately active UC [strong recommendation; quality of evidence low].

We performed a meta-analysis of 11 eligible RCTs with a total of 2156 patients evaluated for 4–12 weeks. 5-aminosalicylates [5-ASA] had a significantly higher efficacy in achieving **clinical remission**

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[RR: 1.56] versus placebo [95% CI: 1.24–1.97]. Similarly, the **clinical response** in 14 studies [total 2025 patients] evaluated at 2–10 weeks was significantly better for 5-ASA [RR: 1.58; 95% CI: 1.35–1.86] with response in 59% of patients receiving 5-ASA compared to 35% of those receiving placebo. The efficacy of 5-ASA on **endoscopic response** as evaluated in four RCTs with 416 patients investigated after 4–12 weeks was better with 5-ASA [RR: 1.73; 95% CI: 1.0–3.0]. 5-ASA was generally very well tolerated; the serious adverse event [SAE] rate evaluated in 13 studies with 2141 patients for a maximal follow-up of 12 weeks was 6.1% versus 9% in the placebo arms [RR: 0.81; 95% CI: 0.47–1.38].

The quality of evidence was globally evaluated as low due to significant heterogeneity and possible publication and reporting bias for certain outcomes [SoF Table 1, available as Supplementary data at *ECCO-JCC* online].

A Cochrane meta-analysis confirmed the similar efficacy of once-daily or more frequent dosing regimens across multiple studies.[29] This meta-analysis did not show any apparent differences in outcomes between different formulations of 5-ASA considered. Notably, despite discussion regarding differences of colonic distribution of different mesalazine preparations, no significant differences in outcomes were observed in any mesalazine comparator studies. For this reason, patients with mildly active UC who fail to reach remission with appropriately dosed oral 5-ASA are unlikely to achieve remission upon switching to an alternate oral 5-ASA formulation.

The same Cochrane meta-analysis did not find overall evidence for superior efficacy of higher total daily doses across multiple dose-ranging trials when compared with standard licensed doses of the same formulation.[29] Subgroup evaluation of the ASCEND trials suggested a benefit of 4.8 g/day of a polymer-coated formulation of mesalazine [with pH-dependent release] compared to 2.4 g/day in patients with more active disease or in those with prior treatment with corticosteroids, oral 5-ASA,

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rectal therapies, or multiple UC medications.[30–32] Likewise, a post-hoc analysis of ASCEND data also showed greater rates of mucosal healing in the 4.8 g/day group than in the 2.4 g/day group.[33] In contrast, subgroup analysis restricted according to disease severity did not reveal any differences in outcomes between 4.8 g/day and 2.4 g/day in trials of a pH-dependent multimatrix (MMX) 5-ASA preparation.[29,34]

Recommendation 2

We recommend topical [rectal] 5-ASAs at a dose of ≥ 1 g/d for the induction of remission in active distal colitis [strong recommendation, low-quality evidence].

We identified eight suitable studies that assessed a dose of ≥ 1 g topical 5-ASA per day for 2–8 weeks that we used for meta-analysis [SoF Table 2, available as Supplementary data at *ECCO-JCC* online].[35–42] All studies required endoscopic confirmation of rectal inflammation but varied in the maximum proximal limit of disease extent permitted [from a maximum of 20 cm from the anal verge to no upper limit]. There was a significant increase in **clinical response** and **clinical remission** when compared with placebo-treated patients [RR: 2.46; 95% CI: 2.01–3.01 and RR: 3.56; 95% CI: 2.08–6.09, respectively]. In addition, **endoscopic response** in five studies that assessed 1 g 5-ASA daily for 2–8 weeks as induction therapy in distal colitis was significantly more frequently achieved in patients treated with 5-ASA than those treated with placebo [RR: 2.75; 95% CI: 2.04–3.7]. No significant differences in **SAEs** between topical 5-ASA treatment and placebo were observed [RR: 0.26; 95% CI: 0.03–2.29].

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Overall, the quality of available evidence was classified as low. Despite this, our recommendation is strong considering the extensive clinical experience corroborating efficacy and very few SAEs related to topical 5-ASA administration.

Recommendation 3

We suggest the use of oral 5-ASAs [≥ 2 g/d] combined with topical [rectal] 5-ASAs over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent [weak recommendation; very low-quality evidence].

Only a few trials were retrieved that compared the use of oral 5-ASA combined with topical 5-ASA versus oral 5-ASA as monotherapy for induction of remission in adult patients with active UC [SoF Table 3, available as Supplementary data at *ECCO-JCC* online].[43–46] In all of these studies, the desirable effects of 5-ASA combined therapy [compared with oral monotherapy] probably outweigh the undesirable effects of this intervention, although the level of uncertainty is high.

Two trials compared these two therapeutic strategies for **clinical response** in patients with disease of at least rectosigmoid extent.[43,44] The trials were heterogeneous in terms of study design, 5-ASA doses, definition of clinical activity, and definition of clinical improvement. In the pooled analysis, no significant advantage of combined therapy over 5-ASA monotherapy in clinical response was observed [RR: 1.1; 95% CI: 0.95–1.27].

Four trials addressed whether combined 5-ASA therapy is superior to oral monotherapy in inducing **clinical remission** in active UC.[43–46] These studies included 322 patients and treatment duration was 3–8 weeks. All trials were heterogeneous in terms of patient characteristics, criteria used to define disease activity and remission, doses, and 5-ASA regimens. There was a serious inconsistency of

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evidence [I^2 = 71%] and a serious risk of bias as the methods of sequence generation and allocation concealment were unclear in three of four studies. The RR of obtaining clinical remission between combined [oral and topical] 5-ASA treatment versus oral monotherapy was 1.45 [95% CI: 0.98–2.13].

There was only one trial on the influence of combined versus oral 5-ASA therapy on endoscopic activity of UC.[44] Patients receiving 2 g of 5-ASA orally plus 2 g of 5-ASA enemas more frequently achieved endoscopic remission than those treated with 4 g of 5-ASA orally plus placebo enemas. However, the difference was not statistically significant [RR: 1.21; 95% CI: 0.91–1.61]. The quality of evidence for this outcome was downgraded because of serious indirectness [the study assessed endoscopic remission, instead of the outcome of interest, which was an **endoscopic response**] and imprecision [only 77 events in the study].

It is difficult to compare the safety of combined versus oral 5-ASA induction treatment since only one trial addressed this question with very sparse data.[43] Only four **SAEs** were detected; 3/71 patients in the combined treatment group and 1/56 patients in the oral 5-ASA plus placebo enema group experienced SAEs [RR: 2.37; 95% CI: 0.25–22.14]. In parallel to this very serious imprecision, there was also a serious risk of bias. Therefore, the quality of the data for this outcome was assessed to be very low.

Overall, we felt that the trend towards better outcomes for combined therapy, clinical experience, and the low cost and risk of the intervention all justified a weak recommendation in favour of combined therapy in patients for whom combined therapy was acceptable.

Topical corticosteroids

Recommendation 4

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We recommend using topical [rectal] steroids for the induction of remission in patients with active distal colitis [strong recommendation, very low-quality evidence].

The use of topically administered steroids has been long established for the induction of remission in patients with proctitis and distal colitis. Topically applied steroids offer the advantage over systemic steroids of a more targeted treatment with fewer systemic side effects; however, topical treatments may be poorly accepted by some patients due to the route of administration.

Several systematic reviews have been conducted on this topic,[47–53] but none included all of the available RCT evidence that was identified here. Therefore, we performed a meta-analysis of five RCTs that compared topical steroids with placebo [SoF Table 4, available as Supplementary data at *ECCO-JCC* online].[54–58] Topical steroids were superior to placebo in induction of **clinical remission** [pooled RR: 2.12; 95% CI: 1.48–3.06], **clinical response** [RR: 2.18; 95% CI: 1.58–3.01], and **endoscopic response** [RR: 1.44; 95% CI: 1.21–1.70]. **SAEs** did not occur more frequently compared to placebo [RR: 0.68; 95% CI: 0.10–4.40]. The number of patients included in each study was quite low and the quality of evidence was very low. This was due to indirectness and imprecision identified for the SAE outcome [a critical outcome, although other critical outcomes were judged to have high-quality evidence]. Overall, we believe that the experience with topical steroids in clinical practice, the favourable balance between their potential benefits and harms (there was no statistically significant difference in adverse events [AE] between topical steroids versus placebo), and their low cost support the recommendation of topical steroids as an option for induction of remission in patients with active UC.

Recommendation 5

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We suggest treatment with topical [rectal] 5-ASAs over topical [rectal] steroids for induction of remission in patients with active distal UC [weak recommendation, very low quality of evidence].

The effect of treatment with topical 5-ASAs at a dose ≥ 1 g/day or topical steroids [suppositories or enemas] for induction of remission in adult patients with active distal UC has been investigated in 13 studies.[38,59,68–70,60–67] We performed a meta-analysis of these studies, which included a total of 1395 patients treated with topical 5-ASA at ≥ 1 g/day or topical steroids [suppositories or enemas], with outcomes captured at 2–8 weeks [SoF Table 5, available as Supplementary data at *ECCO-JCC* online].

Topical 5-ASAs were superior for the induction of **clinical remission** [RR: 1.36; 95% CI: 1.19–1.56] but were not significantly more effective than topical steroids in inducing **clinical response** [RR: 1.09; 95% CI: 0.97–1.22]. In five studies[65–67,71,72] including 376 patients followed for 2–4 weeks, **endoscopic response** was equally likely to be achieved with either topical 5-ASA or topical steroids [RR: 1.08, 95% CI: 0.82–1.44]. In nine studies[60,62–66,69,71,72] including 1306 patients, the rates of **SAEs** did not differ between topical 5-ASAs or topical steroids [RR: 1.21; 95% CI: 0.47–3.08]. Overall, the quality of evidence was rated as very low.

Although patients should generally be treated with a single topical agent, there is some [very limited] evidence to suggest that combination rectal 5-ASA and rectal corticosteroids may be of benefit. This may be appropriate for some patients who fail to respond to initial rectal therapy.[66] It is also important to be aware of differences between preparations in terms of delivery systems and formulations, all of which may have differences in patient acceptability. It is appropriate to offer a patient a trial of an alternative preparation if they are unable to tolerate an initial choice.

Colonic-release corticosteroids

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Recommendation 6

We suggest the use of colonic-release corticosteroids for induction of remission in patients with active mild-to-moderate UC [weak recommendation, low quality of evidence].

The effect of treatment with colonic-release corticosteroids using once-daily budesonide MMX 9 mg for induction of remission in adult patients with active mild-to-moderate UC has been investigated in three studies[73–75] [SoF Table 6, available as Supplementary data at *ECCO-JCC* online]. A total of 542 patients treated with colonic-release corticosteroids were included and followed for 8 weeks. Colonic-release corticosteroids were superior to placebo in inducing **clinical remission** and **clinical response** [RR: 2.86; 95% CI 1.62–5.04 and RR: 1.46; 95% CI: 1.11–1.93, respectively]. In two studies[73,74] including 510 patients followed for 8 weeks, **endoscopic response** was more likely to be achieved with colonic-release corticosteroids in comparison with placebo [RR: 1.43; 95% CI: 1.10–1.84]. In all three studies, the rates of **SAEs** and of any AEs did not differ between colonic-release corticosteroids and placebo [RR: 0.88; 95% CI: 0.33–2.41 and RR: 1.04; 95% CI: 0.79–1.37, respectively]. The low number of SAEs resulted in a low quality of evidence for this critical endpoint due to imprecision.

A pooled analysis of data from both phase 3 trials showed a combined clinical and endoscopic remission rate of 17.7% for budesonide MMX 9 mg/day versus 6.2% for placebo (Odds Ratio [OR]: 3.3; 95% CI: 1.7–6.4).[76] While subgroup analysis of these pooled data revealed that this benefit was seen in patients with left-sided colitis, the difference between drug and placebo was not statistically significant in those with more extensive disease.

Unlike other therapies, including 5-ASA, no data exist for the role of budesonide MMX as a maintenance therapy. This suggests that the most appropriate use of budesonide MMX may be in patients with mildly-to-moderately active disease who are not responding to or are intolerant to

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optimised 5-ASA therapy. A RCT comparing budesonide MMX 9 mg/day with placebo in patients with mildly-to-moderately active UC despite oral 5-ASA therapy revealed a significant improvement in the primary endpoint of combined clinical and endoscopic remission [13% vs 7.5%; p = 0.049) and histological healing in the treatment arm [27% vs 17.5%; p = 0.016].[77]

Immunomodulators

Recommendation 7

We suggest against the use of thiopurines as monotherapy for the induction of remission in patients with active UC [weak recommendation, very low quality of evidence].

Two studies have reported on the use of azathioprine as monotherapy compared to placebo for induction of remission in patients with UC.[78,79] Overall, only 130 patients in two RCTs were analysed and assessed for **clinical remission** after 1–4 months, with azathioprine given alongside a concomitant course of corticosteroids. We performed a meta-analysis of these studies and did not observe a difference between azathioprine and placebo for induction of clinical remission [RR: 1.22; 95% CI: 0.79–1.88] [SoF Table 7, available as Supplementary data at *ECCO-JCC* online]. No placebo-controlled data on clinical response, endoscopic response, or SAEs were available.

It should be noted that due to the relatively slow onset of action of azathioprine, it may be appropriate to initiate azathioprine in patients with active disease where maintenance therapy with azathioprine is planned, but only when given alongside an effective induction agent.

We did not identify any studies using other thiopurines [mercaptopurine or thioguanine] for the induction of remission. Due to their related mechanism of action, we extend our recommendation against the use of azathioprine in induction of remission across the entire thiopurine class.

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4.2: Maintenance of remission in mildly-to-moderately active ulcerative colitis

5-ASAs

Recommendation 8

We recommend the use of oral 5-ASAs at a dose ≥ 2 g/day for maintenance of remission in UC patients [strong recommendation; very low quality of evidence].

We identified two RCTs involving 306 participants with 48–52 weeks of follow up that provided evidence relevant to our PICO question. We synthesised these in a meta-analysis [SoF Table 8, available as Supplementary data at *ECCO-JCC* online].

For **clinical remission**, there was moderate-quality evidence that oral 5-ASA [≥ 2 g/d] was statistically significantly superior to placebo for maintaining remission in adult patients with UC [RR: 1.54; 95% CI: 1.11–2.14]. For **endoscopic remission**, while there was moderate-quality evidence favouring the use of 5-ASAs, this did not reach significance [RR: 1.20; 95% CI: 1.00–1.44]. Only one RCT contributed evidence [of very low quality] for **SAEs**.[80] Treatment with oral 5-ASA [≥ 2 g/d] was associated with statistically significantly fewer SAEs [RR: 0.41; 95% CI: 0.23–0.71].

Although the quality of evidence was judged to be overall very low [due to problems with data for SAEs], we nonetheless felt it appropriate to make a strong recommendation given the safety and relatively low cost of this intervention. An additional consideration may be the reported potential chemopreventive benefits of maintenance 5-ASA treatment, although this finding has been inconsistently reported in the literature and may reflect selection bias seen in referral centre-based cohorts.[81]

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Recommendation 9

We suggest the use of topical [rectal] 5-ASA for the maintenance of remission in patients with distal UC [weak recommendation, very low-quality evidence].

We identified four placebo-controlled trials that assessed topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis [SoF Table 9, available as Supplementary data at *ECCO-JCC* online].[82–85] Doses used ranged between 1 g three times weekly and 1 g daily administered as suppositories or enemas over a period of 12 months [three studies] to 24 months [one study]. The quality of evidence was rated as low due a to serious risk of bias and inconsistency. The same studies were identified in a previous Cochrane review.[86] The use of topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis was significantly superior in maintenance of **clinical remission** compared with placebo [RR: 2.22; 95% CI: 1.26–3.90]. For the **maintenance of endoscopic remission**, data on the use of 1 g 5-ASA enemas in distal UC or proctitis are available for just 25 patients treated over the course of 12 months; 5-ASA was superior to placebo [RR: 4.88; 95% CI: 1.31–18.18].[87]

These studies did not report data on SAEs. A previous Cochrane Review found no significant difference in the proportion of patients experiencing AEs or in the rate of withdrawals due to AEs with topical 5-ASA compared with placebo.[86] Although the level of evidence is very low, our recommendation is strong based on the long clinical experience of efficacy and minimal side effects of rectal formulations of 5-ASA along with the low cost of this intervention. It is important to consider patient acceptability; for some patients, the use of the rectal route for maintenance therapy provides significant advantages both in reducing systemic exposure to drugs and avoiding a greater level of immunosuppression. However, the rectal route of administration may present

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challenges for medication adherence,[88] with patients facing practical difficulties in administration and enema retention. Patient support and education may increase adherence; otherwise, alternative formulations or drugs should be considered.

Immunomodulators

Recommendation 10

We recommend monotherapy with thiopurines for the maintenance of remission in patients with steroid-dependent UC or who are intolerant to 5-ASAs [strong recommendation, moderate quality of evidence].

We identified four placebo-controlled RCTs on maintenance treatment with azathioprine in patients with UC who were steroid-dependent or intolerant to 5-ASA [SoF Table 10, available as Supplementary data at *ECCO-JCC* online].[78,79,89,90] In 232 patients followed for one year, azathioprine was superior [56%] to placebo [35%] for the maintenance of clinical remission [RR: 1.59; 95% CI: 1.19–2.11]. No placebo-controlled data on endoscopic or histologic remission, sustained clinical remission, or SAEs were available. In contrast to current clinical trials, different disease activity indices and endpoint definitions were used. Hence, indirect comparisons with novel and potentially more potent agents are difficult. Nevertheless, large-scale cohort studies highlighted the apparent clinical benefit of thiopurine monotherapy.[91] Since we do not recommend the use of thiopurines for induction of remission, it is important that any maintenance strategy with thiopurines is planned alongside an effective induction agent. We did not identify any RCTs of thiopurines other than azathioprine, but due to their closely related pharmacology, we extend our recommendation across the drug class.

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Significant safety concerns do exist with the use of thiopurines. This is particularly true in patients > 65 years; use of thiopurines should be discouraged in this age group.[8,92–94]

No evidence supports the use of methotrexate for the maintenance of remission in UC.[95] A RCT of methotrexate against placebo failed to demonstrate any advantage in terms of steroid-free clinical remission.[96]

5. Medical management of moderately-to-severely active ulcerative colitis

5.1: Induction of remission in moderately-to-severely active ulcerative colitis

Systemic corticosteroids

Recommendation 11

We recommend oral prednisolone for induction of remission in non-hospitalised patients with moderately-to-severely active UC [strong recommendation; very low quality of evidence].

Despite a limited evidence base, the use of systemic corticosteroids for the induction of remission in moderately-to-severely active UC is well established in clinical practice. The limited evidence is due in part to the large effect size and limited alternative options at the time of the original RCTs.[97,98] A previous meta-analysis[99] included five placebo-controlled RCTs, although only two of them[97,98] used standard systemic corticosteroids. Therefore, we performed a meta-analysis of just these two studies and calculated a RR of 2.83 [95% CI: 1.79–4.46] for the induction of **clinical remission**. The quality of evidence was rated as very low, due to a serious risk of bias, indirectness, and imprecision

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[in part since the number of patients included in each study was low] [SoF Table 11, available as Supplementary data at *ECCO-JCC* online].

No information regarding AEs with steroid treatment was available in these two studies. Other studies established the side-effect profile of corticosteroids in both short courses and also upon longer-term exposure in both UC and Crohn's disease.[21,100] Due to the potential for side effects, some of which are irreversible, corticosteroid-free remission represents a desired outcome for patients.[101,102]

Overall, we believe that the ample experience with systemic steroids in clinical practice and the favourable balance between their potential benefits and harms [when used over limited periods] support the recommendation of oral prednisolone [or another equivalent systemic steroid agent, such as methylprednisolone or prednisone] as an option for induction of remission in patients with moderately-to-severely active UC. For these reasons, our recommendation is graded as strong, despite the quality of evidence being very low.

A prior meta-analysis identified six RCTs that compared systemic prednisolone with budesonide and found a significantly higher chance of induction of remission but increased steroid-related AEs with prednisolone.[99] However, none of these RCTs used a colonic-release budesonide formulation. We restrict our recommendations for budesonide MMX in mild-to-moderately active disease and prednisolone in moderately-to-severely active UC to reflect the study populations of the RCTs identified and the likely risk-benefit profile in these different populations.

It is important to note that there are no efficacy data supporting the use of corticosteroids as maintenance therapies and very limited data on the ability of these drugs to achieve **endoscopic response**. Additionally, longer-term corticosteroid exposure is associated with significant safety concerns. Due to this, along with the availability of drugs with proven ability to maintain

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corticosteroid-free remission, we advise monitoring of corticosteroid exposure in patients with UC. Corticosteroid-sparing agents should be initiated for any patient showing corticosteroid-refractory disease or intolerance of or contraindication to corticosteroids. Additionally, courses of corticosteroids should be restricted to a maximum of 3 months and therapy with a corticosteroid-sparing agent should be considered for any patient who requires more than a single course of systemic corticosteroids in a year or experiences a disease flare upon steroid tapering.

Anti-TNF agents

Recommendation 12

We recommend treatment with anti-TNF agents [infliximab, adalimumab, and golimumab] to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate-quality evidence].

We identified nine suitable RCTs that compared anti-TNF agents [infliximab, adalimumab, golimumab] with placebo in patients with moderately-to-severely active UC [SoF Table 12, available as Supplementary data at ECCO-JCC online].[103–111] Patient eligibility required an inadequate response to or intolerance of conventional therapy, which were defined as corticosteroids, immunomodulators, or both in most studies, although three RCTs also permitted inadequate response to or intolerance of oral 5-ASAs alone.[103–105] Our meta-analysis revealed evidence of efficacy for induction of **clinical remission** [RR: 2.23; 95% CI: 1.81–2.76] and **clinical response** [RR: 1.56; 95% CI: 1.38-1.76]. We found data supporting efficacy for mucosal healing [RR: 1.49; 95% CI: 1.32–1.68], which is closely related to but defined differently from the outcome of interest used in this guideline [endoscopic response]; evidence was therefore downgraded due to indirectness. There was no difference in terms of AEs when analysed regardless of treatment duration [RR: 0.84;

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95% CI: 0.64–1.09]. Safety data for anti-TNF agents from large cohort studies were generally reassuring.[93,94,112]

Studies that directly compared anti-TNF agents are not available. Two network meta-analyses[113,114] that performed indirect comparisons concluded that infliximab is superior to adalimumab for the induction of **clinical remission** [OR: 2.10; 95% CI: 1.21–3.64[113] and OR: 2.10; 95% CI: 1.16–3.79[114]]. The first network meta-analysis also concluded that infliximab is superior to adalimumab and golimumab for induction of **clinical response** [OR: 2.01; 95% CI: 1.36–2.98 and OR: 1.67; 95% CI: 1.08–2.59, vs adalimumab and golimumab, respectively] and for induction of mucosal healing [OR: 1.87; 95% CI: 1.26–2.79 and OR: 1.75; 95% CI: 1.13–2.73, vs adalimumab and golimumab, respectively].[113]

For patients with a history of prior failure of biologic therapy, there are limited data to guide treatment selection. Subgroup analysis of a phase 3 trial suggests that the clinical effects of induction therapy with adalimumab were markedly lower in patients with prior anti-TNF agent exposure [and non-significantly different from placebo].[110] A previous systematic review of cohort studies identified eight studies that reported the efficacy of adalimumab when used after infliximab in UC. However, meta-analysis was not possible due to study heterogeneity.[115] In patients with a history of prior infliximab therapy randomised to either adalimumab or vedolizumab, rates of clinical remission and endoscopic response were not significantly different.[116] There are extremely limited data on the use of anti-TNF agents in other biologic sequences.

A key question is whether to combine an anti-TNF agent with an immunomodulator. The combination of infliximab with azathioprine is more effective than infliximab alone.[117] Similar RCT-level data do not exist for adalimumab in combination with thiopurine therapy in UC, although cohort studies suggest a possible benefit for this combination[118] and pharmacokinetic benefits have been reported in patients with Crohn's disease.[119] For patients experiencing loss of response to a

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first anti-TNF agent used as monotherapy and with evidence of anti-drug antibodies, there is clear RCT evidence in favour of addition of a thiopurine to prevent formation of anti-drug antibodies to the second anti-TNF agent.[120]

The optimal time point for the introduction of anti-TNF therapy has yet to be defined. Unlike in Crohn's disease, no post-hoc analysis has demonstrated increased efficacy of anti-TNF agents used early in the UC disease course. Factors predicting severe or complicated disease, such as young age at first diagnosis, extensive disease, and high inflammatory burden, have been proposed to identify patients who may benefit from early treatment escalation,[121] although the benefits of this approach have not been demonstrated in any strategy trial.

Vedolizumab

Recommendation 13

We recommend treatment with vedolizumab for the induction of remission in patients with moderately-to-severely active UC who have inadequate response or intolerance to conventional therapy [strong recommendation, low quality of evidence].

Two placebo-controlled RCTs were identified that addressed our PICO question. These included 620 patients with moderately-to-severely active UC treated with vedolizumab or placebo; induction of clinical remission, induction of clinical response, and SAEs were reported.[122,123] Patients were followed up to 6–10 weeks [SoF Table 13, available as Supplementary data at ECCO-JCC online].

We included these two studies in a meta-analysis. **Clinical remission** was achieved more often in patients receiving vedolizumab compared to placebo [RR: 2.14; 95% CI:1.03–4.43]. Although the direction of effect for **clinical response** was the same as for clinical remission, the difference

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between patients treated with vedolizumab and those receiving placebo was not significant [RR: 1.51; 95% CI: 0.99–2.29]. Rates of **SAEs** in patients treated with vedolizumab were not significantly different from those receiving placebo [RR: 0.71; 95% CI: 0.39–1.30]. Safety data from large cohort studies also confirmed this favourable safety assessment.[112]

Evidence was also sought for endoscopic response and biochemical remission; however, data were insufficient. Of note, rates of endoscopic remission at week 6 in the GEMINI I phase 3 induction study were 40.9% for vedolizumab-treated patients compared with 24.8% for placebo-treated patients [p = 0.001].[122] In contrast, endoscopic remission rates at week 10 in a Japanese phase 3 induction study did not differ significantly between vedolizumab- and placebo-treated patients [36.6% vs 30.5%, p = 0.32].[123]

The overall quality of evidence was low. The quality of evidence was low for clinical remission due to serious inconsistency and imprecision. The quality of evidence was moderate for clinical response due to serious inconsistency. The inconsistency for both outcomes was due to heterogeneity in outcomes between the two RCTs. The quality of evidence for SAEs was moderate due to serious imprecision. However, the overall recommendation was graded as strong considering the overall evidence available combined with the favourable safety profile of vedolizumab in both RCT and cohort studies.

Tofacitinib

Recommendation 14

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We recommend treatment with tofacitinib to induce remission in patients with moderate-to-severe UC who have inadequate response or intolerance to conventional therapy [strong recommendation, moderate quality of evidence].

We performed a meta-analysis of data from two RCTs relevant to our PICO question. These included 1220 patients with moderate-to-severe UC who previously had an inadequate response, loss of response, or were intolerant to either conventional therapy [mesalamine plus steroids or thiopurines] or a biologic agent who were treated with tofacitinib or placebo [SoF Table 14, available as Supplementary data at ECCO-JCC online].[124,125] There was evidence for efficacy in induction of **clinical response** [RR: 1.79; 95% CI: 1.49–2.14], **clinical remission** [RR: 3.26; 95% CI: 1.95–5.43], and **endoscopic response** [RR: 5.18; 95% CI: 2.12–12.69]. However, the evidence regarding endoscopic response was downgraded due to indirectness and imprecision [low number of events]. Data on biochemical remission were insufficient. SAEs were comparable [RR: 0.70; 95% CI: 0.45–1.08], although the evidence was also downgraded due to imprecision.

Further safety data are available from post-marketing studies of tofacitinib [discussed under maintenance therapy below], which should be considered when deciding upon choice of induction therapy. The potential benefits of an oral route of administration and the lack of immunogenicity should also be considered. A previous meta-analysis of RCTs on tofacitinib showed similar positive data for clinical and endoscopic endpoints in both the subgroup of patients naïve to anti-TNF agents and the subgroup with prior anti-TNF agent exposure.[126] There were no significant differences in estimates of effect sizes between these subgroups. This was reflected in the findings of indirect network meta-analyses that did not find evidence of a statistical difference between tofacitinib and anti-TNF agents or ustekinumab for clinical and endoscopic outcomes in patients naïve to biologic therapy,[113,127] but suggest a possible benefit over adalimumab or vedolizumab for patients with prior anti-TNF agent exposure.[127]

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Ustekinumab

Recommendation 15

We recommend treatment with ustekinumab for the induction of remission in patients with moderately-to-severely active UC with inadequate response or intolerance to conventional therapy. [strong recommendation, moderate quality of evidence].

A single RCT compared ustekinumab with placebo for induction therapy in patients with moderately-to-severely active UC [SoF Table 15, available as Supplementary data at ECCO-JCC online].[128] Patients were required to have not responded to or been intolerant to prior biologic or conventional therapy [defined as corticosteroid or thiopurines], or both, or have corticosteroid-dependent disease. Of these, 51.1% of randomised patients had previously failed treatment with an alternative biologic, including 16.6% who failed treatment with both an anti-TNF agent and vedolizumab. The study demonstrated the benefit of ustekinumab [6 mg/kg] over placebo in induction of **clinical remission** [15.5% vs 5.3%; RR: 2.91; 95% CI: 1.72–4.94], **clinical response** [61.8% vs 31.3%; RR: 1.97; 95% CI: 1.64–2.37], and **endoscopic improvement** [27.0% vs 13.8%; RR: 1.96; 95% CI: 1.41–2.72].

At completion of induction, the change in mean IBDQ score from baseline was greater in those receiving ustekinumab [6 mg/kg] than in those receiving placebo [35.0 vs 16.16, $p < 0.001$]. Median change in faecal calprotectin from baseline also showed a more significant reduction in the treatment arm [-1368.26 vs 17.92; $p < 0.001$]. **SAEs** did not differ between ustekinumab [6 mg/kg] and placebo [5.2% vs 7.9%; RR: 0.67; 95% CI: 0.39–1.17].

Clinical and endoscopic benefit compared with placebo was observed for patients with and without prior biologic failure. An indirect network meta-analysis did not reveal a statistical difference

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between ustekinumab and anti-TNF agents or tofacitinib for clinical and endoscopic outcomes in patients naïve to biologic therapy, but suggested a possible benefit of ustekinumab over adalimumab or vedolizumab for patients with prior anti-TNF exposure.[127]

5.2: Maintenance of remission of moderately-to-severely active ulcerative colitis

Anti-TNF agents

Recommendation 16

We recommend anti-TNF agents [infliximab, adalimumab, or golimumab] for the maintenance of remission in patients with UC who responded to induction therapy with the same drug [strong recommendation, high quality evidence].

We performed a meta-analysis of data extracted from 10 placebo-controlled RCTs of anti-TNF agents [infliximab, golimumab, adalimumab] for the maintenance of remission in adult patients with moderately-to-severely active UC [SoF Table 16, available as Supplementary data at ECCO-JCC online].[103–111,129] Anti-TNF agents were effective for the maintenance of **clinical remission** [RR: 1.98; 95% CI: 1.60–2.45], **steroid-free clinical remission** [RR: 2.86; 95% CI: 1.67–4.90], **improvement in QoL** [RR: 1.71; 95% CI: 1.27–2.32] and **sustained clinical remission** [RR: 2.76; 95% CI: 1.78–4.28]. The risk of **SAEs** was not different between anti-TNF agents and placebo [RR: 0.84; 95% CI: 0.64–1.09]. Evidence was also sought for endoscopic remission and biochemical remission; however, data were insufficient. Large-scale cohort studies support the safety of these drugs.[93,94,112]

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Recommendation 17

In UC patients who have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of therapeutic drug monitoring to improve clinical outcomes.

Multiple studies have shown an association between trough levels of biological agents, including anti- TNF agents,[130–135] vedolizumab,[136–138] and ustekinumab[139] and clinical outcomes in UC. Nonetheless, these studies were all retrospective analyses and cannot confirm any causal effect or suggest a benefit of trough-level based dose adjustment for improvement of response to biologics in patients with persistent disease activity. Retrospective analyses of mixed cohorts of patients with IBD experiencing loss of response to anti-TNF agents have shown that measurement of adequate infliximab or adalimumab drug levels appears to correlate well with patients who do not respond to subsequent dose escalation and to patients who do respond to switching to non-anti-TNF therapies.[140–142] These retrospective data suggest that decisions informed by drug monitoring may be more likely to be successful than clinically guided decision making alone,[141] but this requires validation in a prospective study.

The same challenges and arguments around the need to demonstrate benefit and not just association apply to discussions around the use of prospective monitoring of drug levels to guide dosing in patients who are not experiencing loss of response. One study, published in abstract only, randomised 371 participants with UC who had responded to induction therapy with adalimumab to receive adalimumab at standard dose [40 mg every other week], high dose [40 mg every week], or dosing guided by therapeutic drug monitoring.[143] The therapeutic drug monitoring arm was not powered to demonstrate superiority and was considered exploratory. There was a non-significant trend towards higher rates of clinical remission amongst responders to induction therapy who were randomised to receive drug-monitoring guided dosing compared with standard dose [36.5% vs 29%].

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Overall, given the lack of appropriate prospective studies, we were unable to make a recommendation [SoF Table 17, available as Supplementary data at ECCO-JCC online] and we suggest further research in this area.

Vedolizumab

Recommendation 18

We recommend vedolizumab for maintenance of remission in patients with UC who responded to induction therapy with vedolizumab [strong recommendation, moderate-quality evidence].

We identified three RCTs that included 441 patients treated with intravenous vedolizumab or placebo that reported on maintenance of clinical remission and sustained clinical remission in adult patients with moderately-to-severely active UC who responded to induction therapy [SoF Table 18, available as Supplementary data at ECCO-JCC online].[122,123,144,145] Patients in these trials were followed up for 52–60 weeks. We performed a meta-analysis of results from these trials. **Clinical remission** was more common in induction-responders who subsequently received vedolizumab compared with placebo [RR: 2.37; 95% CI: 1.74–3.23]. Likewise, **sustained clinical remission** was also more common in patients receiving vedolizumab maintenance therapy compared with placebo [20.7% vs 9.4%; RR: 2.16; 95% CI: 1.34–3.50]. The quality of evidence for these outcomes was moderate to high. The rate of **SAEs** across five studies involving 1288 patients was not significantly different between vedolizumab and placebo [RR: 0.71; 95% CI: 0.39–1.30]. The quality of evidence for this outcome was moderate due to serious imprecision arising from sparse data. Nevertheless, the safety profile of vedolizumab has been established in a large cohort study.[112] In particular, the

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rate of serious infections in patients with UC appeared lower in those treated with vedolizumab than with anti-TNF agents, after adjusting for baseline differences [including comorbidities].

More recently, a double-dummy placebo-controlled RCT evaluated both intravenous and subcutaneous preparations of vedolizumab in patients with moderately-to-severely active UC who had responded to open-label intravenous vedolizumab induction therapy.[144] **Clinical remission**, **endoscopic improvement**, and **sustained clinical remission** were significantly more frequently observed with subcutaneous vedolizumab than with placebo. The study was not powered to compare intravenous and subcutaneous preparations, although all outcomes were numerically similar between these two groups. SAEs occurred at similar frequencies in all three groups and no distinct safety signals were observed with the subcutaneous preparation.

Recommendation 19

We suggest the use of vedolizumab rather than adalimumab for the induction and maintenance of remission in patients with moderately-to-severely active ulcerative colitis [weak recommendation, low level of evidence].

One RCT compared the efficacy and safety of vedolizumab with those of adalimumab over a 1-year period in patients with moderately-to-severely active UC [SoF Table 19, available as Supplementary data at ECCO-JCC online].[146] A significantly higher percentage of patients in the vedolizumab group than in the adalimumab group achieved **clinical response** [RR: 1.46; 95% CI: 1.29–1.67], **clinical remission** [RR: 1.39; 95% CI: 1.10–1.76), and **endoscopic remission** [RR: 1.43; 95% CI: 1.17–1.75]. There was a numeric trend in favour of vedolizumab for **biochemical remission** [RR: 1.22; 95% CI: 0.96–1.54]. Corticosteroid-free clinical remission occurred in a numerically lower percentage of

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patients in the vedolizumab group than in the adalimumab group [RR: 0.58; 95% CI: 0.32–1.05]. Of note, the quality of evidence for steroid-free clinical remission was low, as evidence relied on sparse data and the confidence intervals were very wide. Incidence rates of infections and serious infections occurred at similar frequencies with vedolizumab and with adalimumab [RR: 0.80; 95% CI: 0.55–1.17]. It is important to note that dose escalation was not permitted with either drug, despite evidence of improved maintenance outcomes with dose escalation for both drugs.[122,143,147]

Tofacitinib

Recommendation 20

We recommend tofacitinib for maintaining remission in patients with UC who responded to induction therapy with tofacitinib [strong recommendation, moderate quality of evidence].

We identified one RCT that reported outcomes in 593 patients treated with tofacitinib or placebo as maintenance therapy.[125] For patients who responded to induction therapy, tofacitinib at a dose of 5 or 10 mg twice daily was superior to placebo in maintaining **clinical remission** [RR: 3.37; 95% CI: 2.23–5.10] and **endoscopic remission** [RR: 3.88; 95% CI: 1.90–7.95] in patients with moderate-to-severe UC who had an adequate response to the induction scheme. However, the evidence regarding endoscopic remission was downgraded due to imprecision [low number of events]. **Sustained clinical remission** [RR: 4.71; 95% CI: 2.51–8.84], **corticosteroid-free remission** [RR: 2.54; 95% CI: 1.39–4.65], and improvement in **QoL** [RR: 2.55; 95% CI: 1.93–3.37] were also superior. The evidence regarding corticosteroid-free clinical remission was also downgraded due to imprecision. Data on biochemical remission were insufficient.

SAEs for tofacitinib therapy in RCTs were comparable to placebo [RR: 0.70; 95% CI: 0.45–1.08]. The evidence was again downgraded due to imprecision. However, an increased risk for infections was

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observed [OR: 1.56; 95% CI: 1.18–2.06]. Most of the serious infections were of bacterial origin, including community-acquired pneumonia and urinary tract and skin infections. A separate meta-analysis of the safety profile of Janus kinase inhibitors across multiple inflammatory diseases showed a particularly high risk of viral infections, especially herpes zoster [RR: 6.53; 95% CI: 0.86–49.58].[148] This signal was also observed in a pooled analysis of safety data from the tofacitinib development programme in UC [incidence rate 4.1 events per 100 person-years; 95% CI: 3.1–5.2][149], although most cases were uncomplicated and associated with a single dermatome. This risk appears to be dose dependent and is more common with 10 mg twice daily dosing than 5 mg twice daily.[149] A large cohort study in rheumatoid arthritis suggested that the rates of herpes zoster appear higher with tofacitinib than with anti-TNF agents; this risk appeared to be especially significant in older patients or in those receiving concomitant corticosteroid therapy.[150]

A safety study of tofacitinib in patients with rheumatoid arthritis aged ≥ 50 years and with at least one known cardiovascular risk factor revealed a significantly increased risk of venous thromboembolism [VTE] in patients treated with 10 mg twice daily tofacitinib compared with patients treated with anti-TNF agents. This risk was not observed in patients treated with 5 mg twice daily tofacitinib.[151] Although data are sparse, VTE has been reported in patients with VTE risk factors who participated in the UC development programme.[152] Considering these findings, the European Medicines Agency recommended using tofacitinib at the lowest efficacious dose and avoiding tofacitinib 10 mg twice daily as maintenance treatment for patients with known VTE risk factors. In this regard, 140 UC patients treated with tofacitinib 10 mg twice daily for at least 2 consecutive years and in sustained remission for ≥ 6 months were randomised to continue with the same dose or de-escalate to 5 mg twice daily. After 6 months, clinical remission rates were 77% and 90% for the 5 mg twice daily and 10 mg twice daily groups, respectively. No differences in AEs or SAEs were detected between the two groups, although herpes zoster cases were numerically higher in the 10

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mg twice daily group.[153] Further post-marketing surveillance data suggest that tofacitinib use is also associated with an increased risk of cardiac events and malignancies.[154] Overall, we reiterate the comments made previously that the efficacy data, including in patients with prior anti-TNF exposure, along with the benefits associated with oral dosing and lack of immunogenicity, support our recommendations for tofacitinib as a treatment option in patients with UC, with the risks and benefits to be considered for each patient.

Ustekinumab

Recommendation 21

We recommend ustekinumab for the maintenance of remission in patients with UC who responded to induction therapy with ustekinumab [strong recommendation, moderate quality of evidence].

A single RCT compared ustekinumab with placebo for maintenance therapy in UC in patients who responded to ustekinumab induction therapy.[128] The study revealed that maintenance treatment with ustekinumab at approved dosing of 90 mg subcutaneous every 8 weeks offers benefit when compared with placebo in maintenance of **clinical remission** [RR: 1.82; 95% CI: 1.33–2.49] and maintenance of **steroid-free clinical remission** [RR: 1.79; 95% CI: 1.30–2.47] at week 44. Although data were not available for endoscopic improvement, we used data for the closely related endpoint of **endoscopic remission** and found benefit compared with placebo [RR: 1.79; 95% CI: 1.36–2.36]. There was a reduction in mean faecal calprotectin for those who remained on ustekinumab during the maintenance period [-434.9 vs 813.3]. The benefits of ustekinumab were also reflected by the IBDQ scores in patients who completed the maintenance study [3.9 vs -15.7]. SAEs did not occur more frequently in the treatment arm [5.2% vs 7.9%; RR: 0.67; 95% CI: 0.39–1.17].

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In addition to 8 weekly dosing, the study also evaluated 12 weekly maintenance therapy. Twelve weekly dosing also showed statistically significant superiority over placebo for **clinical remission** [RR: 1.60; 95% CI: 1.16–2.21], **steroid-free clinical remission** [RR: 1.61; 95% CI: 1.16–2.24], and **endoscopic remission** [RR: 1.53; 95% CI: 1.14–2.04]. Compared with 8 weekly dosing, rates were numerically lower, but this did not reach statistical significance. The differences between outcomes with 8 weekly and 12 weekly dosing were greater in patients with a history of prior biologic failure.[128]

6. Conclusion

These recommendations summarise the current evidence on the medical management of adult patients with UC. Gaps were identified during the analysis of the data, which should be addressed by further research. Where evidence is lacking or is very weak and evidence-based recommendations cannot be given, ECCO provides alternative tools, such as Topical Reviews[28,95,155–160] or Position Papers.[161–163] It is important that clinicians use these guidelines within the framework of local regulations and seek to understand and address the individual needs and expectations of every patient. We recognise that constraints on healthcare resources are an important factor in determining whether recommendations can be implemented for patients in many countries. The recommendations outlined here should be used to inform treatment decisions and form part of an overall multidisciplinary treatment plan for patients with UC, which may also encompass psychological, nutritional, and other non-pharmacological interventions. ECCO will disseminate these guidelines by educational activities [i.e., educational platforms, ECCO Workshops, e-learning, and e-Guide] and will support any initiative to integrate ECCO Guidelines into clinical practice; the ECCO e-Guide will primarily serve as a resource to

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examine how the Guideline recommendations can be implemented into daily clinical practice and patient care pathways.[164] The e-Guide addresses important practical issues not addressed here, such as how to monitor for both positive and negative effects of medications. These treatment guidelines will be regularly updated according to the Guideline Committee schedule for the update of Guidelines on the ECCO website. Updates will use the GRADE approach and consider the most recent evidence emerging from clinical research in the field.

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Funding

This project was initiated, funded, and supported by ECCO.

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of JCC, but are also open to public scrutiny on the ECCO website

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Acknowledgements

We thank the ECCO Office for logistical and coordination support; Paul Freudenberger for the literature search; and Torsten Karge for the support on informatics and on the online Guidelines platform. We gratefully thank the EFCCA patient representatives Kirsty Gibson [United Kingdom], Isabella Grosu [Romania], Lucie Lastikova [Czech Republic], Jarkko Lignell [Finland], Edda Svavarsdottir [Iceland], Szajer Daria [Poland] who proactively collaborated in the development of these Guidelines.

We would like to thank and acknowledge the ECCO National Representatives, who acted as external reviewers and reviewed and provided suggestions on the recommendations and supporting text to this document: Filiz Akyüz [Turkey], Raja Atreya [Germany], Giorgos Bamias [Greece], Manuel Barreiro de Acosta [Spain], Dominik Bettenworth [Germany], Ante Bogut [Bosnia and Herzegovina], Garret Cullen [Ireland], Pieter Dewint [Belgium], Mihai Mircea Diculescu [Romania], Srdjan Djuranovic [Serbia], Andrey Dorofeyev [Ukraine], Pavel Drastich

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[Czech Republic], Dana Duricová [Czech Republic], Pierre Ellul [Malta], Adrian Goldiș [Romania], Ana Gutierrez [Spain], Christoph Högenauer [Austria], Tuire Ilus [Finland], Ioannis Kaimakliotis [Cyprus], Željko Krznarić [Croatia], Karin Kull [Estonia], Hendrik Laja [Estonia], Triana Lobaton [Belgium], Gregor Novak [Slovenia], Małgorzata Sładek [Poland], Svetlana Turcan [Moldova], Willemijn van Dop [The Netherlands], Fiona van Schaik [The Netherlands], Ana Isabel Vieira [Portugal], Matti Waterman [Israel], Signe Wildt [Denmark], Henit Yanai [Israel].

Additionally, we would like to thank our colleagues at the European Society of Coloproctology [ESCP] who were invited to participate on the recommendations and statements during the preliminary online vote: Triantafyllos Doulias [UK], Mark Ellebæk [Denmark], Gaetano Gallo [Italy], Rosa Jimenez-Rodriguez [Spain], Ionut Negoi [Romania], Luis Sánchez-Guillén [Spain].

Last, but not least, we would also like to thank and acknowledge the following additional external reviewers who also reviewed and provided suggestions on the recommendations and statements: Mariangela Allocca [Italy], Michele Carvello [Italy], Gabriele Dragoni [Belgium], Daniela Gilardi [Italy], Jost Langhorst [Germany], Lieven Pouillon [Belgium], Iago Rodríguez-Lago [Spain], Simone Saibeni [Italy], Beatriz Sicilia [Spain].

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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