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ECCO Guideline

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

Javier P. Gisbert*[,1], María Chaparro[1], Bram Verstockt[2,3], Peter Kienle[4], Silvia Minozzi[5], Mariangela Allocca[6], Raja Atreya[7], Nicolas Avellaneda[8], Manuel Barreiro-de Acosta[9], Robert Battat[10], Dominik Bettenworth[11,12], Irina Blumenstein[13], Steven R. Brown[14], John P. Burke[15], Flavio Caprioli[16,17], María José Casanova[1], Niki Christou[18], Anthony de Buck van Overstraeten[19], Glen Doherty[20], Piotr Eder[21], Alaa El-Hussuna[22,23], Pierre Ellul[24], Massimo Claudio Fantini[25,26], Federica Furfaro[27,28,29], Thomas Greuter[30], Karl Hazel[31], Stefan Holubar[32], Christina Kapizioni[33], Uri Kopylov[34,35], Rupert W. Leong[36,37], Sezai Leventoglu[38], Jimmy K. Limdi[39,40], Nurulamin M. Noor[41,42], Ioannis Papaconstantinou[43], Georgios Peros[44], Lieven Pouillon[45], Catherine Reenaers[46], Simone Saibeni[47], Carsten Schmidt[48,49], Paula Sousa[50], Laurents P.S. Stassen[51], Mathieu Uzzan[52], Sophie Vieujean[53,54], Eva Visser[55], Pär Myrelid[56,57], Michel Adamina[58], Torsten Kucharzik[59,60]

[1]Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain
[2]Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[3]Department of Chronic Disease and Metabolism, KU Leuven, Leuven, Belgium
[4]Center for Colorectal and IBD-Surgery, Department of General Surgery, University Heidelberg, Heidelberg, Germany
[5]Laboratory of Methodology of Systematic Reviews and Guidelines Production, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[6]Gastroenterology and Endoscopy, IRCCS Hospital San Raffaele and University Vita-Salute San Raffaele, Milan, Italy
[7]First Department of Medicine, Erlangen University Hospital, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[8]IBD Surgical Section, Inmunologia Buenos Aires, Buenos Aires, Argentina
[9]Gastroenterology Department, Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, and Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago, Spain
[10]Division of Gastroenterology, Centre Hospitalier de l'Université de Montréal, Montreal, Canada
[11]CED Schwerpunktpraxis Münster, Münster, Germany
[12]Medical Faculty, University of Münster, Münster, Germany
[13]Goethe University Frankfurt, University Hospital, Department of Gastroenterology, Hepatology and Clinical Nutrition, Frankfurt, Germany
[14]University of Sheffield, Sheffield, United Kingdom
[15]Department of Colorectal Surgery, Beaumont Hospital, Dublin, Ireland
[16]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
[17]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy
[18]Visceral Surgery Department, University Hospital of Limoges, Limoges, France
[19]Department of Colorectal Surgery, Cleveland Clinic Ohio, Cleveland, United States
[20]Department of Gastroenterology, St Vincent's University Hospital & School of Medicine, University College Dublin, Dublin, Ireland
[21]Department of Gastroenterology, Dietetics and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland
[22]Department of Surgery, Odda Hospital, Helse Fonna, Haugesund, Norway
[23]OpenSourceResearch Organisation (OSRC), Aalborg, Denmark
[24]Department of Gastroenterology, Mater dei Hospital, Msida, Malta
[25]Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy
[26]Gastroenterology Unit, AOU di Cagliari, Cagliari, Italy
[27]Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy
[28]Gastroenterology and Gastrointestinal Endoscopy Division, IRCCS San Raffaele Hospital, Milan, Italy
[29]Gastroenterology Unit, Istituti Ospedalieri Bergamaschi, Bergamo, Italy
[30]Department of Gastroenterology and Hepatology, EOC Lugano and Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland
[31]Department of Gastroenterology, Connolly Hospital, Blanchardstown, Dublin, Ireland

[32]Cleveland Clinic Lerner College of Medicine & Case Western Reserve University, Cleveland Clinic Foundation, Cleveland, OH, United States
[33]First Gastroenterology Department, Athens Medical Center, Athens, Greece
[34]IBD Unit, Department of Gastroenterology, Sheba Medical Center, Ramat Gan, Israel
[35]Gray School of Medicine, Tel Aviv University, Tel Aviv, Israel
[36]Department of Gastroenterology, Concord Repatriation General Hospital, Sydney, Australia
[37]Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[38]Department of Surgery, Gazi University School of Medicine, Ankara, Türkey
[39]Section of IBD, Division of Gastroenterology, Northern Care Alliance NHS Foundation Trust, Manchester, United Kingdom
[40]Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Manchester, United Kingdom
[41]Department of Gastroenterology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
[42]Department of Medicine, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom
[43]2nd Department of Surgery, Aretaieion Hospital, National and Kapodistrian University of Athens, Athens, Greece
[44]Chirurgie Zentrum St. Anna, Hirslanden Hospital, Lucerne, Switzerland
[45]Department of Gastroenterology, Imelda Hospital, Bonheiden, Belgium
[46]Gastroenterology Department, Liège University, University Hospital of Sart Tilman, Liège, Belgium
[47]IBD UNIT, Gastroenterology Unit, RHO Hospital, Rho, Milan, Italy
[48]Medical Clinic II, Hospital Fulda, Fulda, Germany
[49]Medical Faculty, Friedrich Schiller University, Jena, Germany
[50]Gastroenterology Department, Unidade Local de Saúde Viseu Dão-Lafões, Viseu, Portugal
[51]Department of Surgery, Nutrim Institute for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands
[52]Gastroenterology Department, Hospital Henri Mondor, APHP, Université Paris-Est Créteil, Créteil, France
[53]Department of Gastroenterology, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[54]Faculty of Medicine, University of Liège, Liège, Belgium
[55]Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[56]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
[57]Clinical Department of Surgery in Linköping, Region Östergötland, Linköping, Sweden
[58]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[59]Department of Internal Medicine and Gastroenterology, Hospital Lüneburg, Lüneburg, Germany
[60]University of Münster, Münster, Germany

*Corresponding author: Javier P. Gisbert, Gastroenterology Department, Hospital Universitario de La Princesa, Diego de León, 62. Madrid 28006, Spain (javier.p.gisbert@gmail.com).

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1. Introduction

Ulcerative colitis [UC] is a chronic inflammatory bowel disease [IBD] characterized 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 summarize the recommended medical treatment for adults with UC.

In 2022, the European Crohn's and Colitis Organisation [ECCO] published new guidelines on the management of UC in two papers focused on the medical and surgical management of the disease.[1,2] For the 2022 UC guidelines, ECCO adopted the Grading of Recommendations Assessment, Development, and Evaluation [GRADE] approach, a systematic process for developing guidelines that addresses how to frame healthcare questions, summarize the evidence, formulate recommendations, and grade their strength and the quality of associated evidence.[3] The present paper represents an update to the 2022 guidelines and focuses specifically on the medical management of UC, while a companion paper developed as part of the same process addresses optimal surgical management [ECCO Guidelines on Therapeutics in Ulcerative Colitis: Surgical Treatment].

For this iteration of the guidelines, we have introduced several new, clinically relevant questions selected by members of the guidelines group, alongside a systematic approach to reviewing and updating previous topics to incorporate new evidence and to reappraise all findings within the context of contemporary practice. We have also introduced several "practice points" to summarize evidence and provide expert recommendations in key areas where the evidence remains limited but clinical decisions are still required. In such instances, where application of the GRADE methodology may be impractical, we adopted an approach based on systematic literature review, expert discussion, and voting to reach consensus recommendations outside the formal GRADE process.

Patients living with UC can have a variable disease course.[4] In this document, we discuss therapeutic approaches stratified by disease severity [mildly-to-moderately active and moderately-to-severely active disease]. Definitions of disease severity are commonly used to establish clinical trial inclusion criteria and may be based on several distinct assessment frameworks.[5] It is also important to remember that these definitions capture severity at a given point in time and may not reflect the cumulative long-term burden of disease experienced by a patient.[6]

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 or distal UC], or disease extending proximal to the splenic flexure [extensive UC].[7] It should be noted that disease distribution can change[4] and that proximal disease extension can be a negative prognostic marker.[8]

2. Methods

The development of these guidelines followed the GRADE workflow, as adopted in previous ECCO guidelines.[3] A panel of 42 experts was selected from an open call according to

criteria based on IBD expertise, scientific background, knowledge of GRADE methodology, and prior contributions to ECCO projects. Additionally, six patients with IBD, selected by the International Federation of Crohn's & Ulcerative Colitis Associations [IFCCA], were invited to participate in discussions. The group was supported by a team of professional methodologists and librarians.

The following two domains for the medical treatment of UC were identified and used as the basis for two working groups according to disease severity: mildly-to-moderately active disease and moderately-to-severely active disease. We recognize that these divisions are somewhat arbitrary, partially overlapping, and inconsistently defined; therefore, close collaboration between the working groups was maintained to ensure that all key topics were appropriately addressed, with the aim of providing guidance applicable across the full 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] framework, which were considered clinically relevant for the medical treatment of UC. These questions were discussed during a series of teleconferences and subsequently finalized at a meeting of the full guideline group held in Vienna in November 2024. Voting on the inclusion of PICO questions was conducted, and only those achieving more than 80% agreement among the panel were included in the next phase of the process. At this meeting, the panellists also ranked the importance of each outcome on a scale from 1 to 9 according to GRADE definitions. Scores of 7-9 indicated outcomes considered critical to patient decision-making; scores of 4-6 indicated outcomes regarded as important but not critical; and scores of 1-3 represented outcomes of limited importance. Agreement among panellists regarding outcome importance was assessed using the Disagreement Index, as described in the RAND/UCLA appropriateness method.[9]

Professional librarians then performed a comprehensive literature search in EMBASE, PubMed/MEDLINE, and the Cochrane Central databases using specific search strings developed for each PICO question [supplementary files available as Supplementary Data at *ECCO-JCC* online]. For PICO questions retained from the 2022 guidelines, the same search string was used as in the previous literature search, with the start date of the database queries set to the end search date of the prior guidelines [February 2020] up to January 2025. For all new PICO questions, the search start date was unrestricted. Two independent consensus group members assessed the relevance of each abstract to the PICO and included or excluded the relevant papers for final data extraction and analysis.

Subsequently, group members systematically reviewed and summarized the evidence on every outcome voted as "important" or "critical," compiling a Summary of Findings [SoF] table for each question. A standard hierarchical approach was adopted, prioritizing recent, high-quality systematic reviews and meta-analyses of clinical trials over individual randomized controlled trials [RCTs] or observational studies. SoF tables, which detail all studies included in the preparation of each recommendation, key data and findings for each outcome of interest, and the corresponding judgements for each quality-of-evidence factor, are provided as Supplementary Material together with full documentation of the evidence assessment process. We present our rating of the certainty of evidence for each outcome, including the risk in the control group; the risk in the intervention group; the meta-analytic effect estimate; the anticipated absolute effects; and any additional relevant information reported in the SoF table, together with the overall rating of the certainty of evidence across outcomes. The SoF tables for PICO questions that were similar to those in the 2022 guidelines were retained without modification, with the outcomes from those guidelines likewise being maintained; these tables are identified as "tidy-up" in the supplementary material, available as supplementary data at *ECCO-JCC* online.

Most of the evidence informing the recommendations in this document was derived from RCTs. The methodologists directly performed the comparisons, using the risk ratio [RR] to measure treatment effects. Study-level RRs with 95% confidence intervals [CIs] were calculated. To synthesize the evidence, forest plots were prepared and pooled effect estimates were calculated using random-effects models following the DerSimonian and Laird approach. All *P*-values were two-tailed, and a *P*-value of <.05 was considered statistically significant for all tests except those assessing heterogeneity.

The certainty of evidence was categorized as high, moderate, low, or very low according to the GRADE methodology.[3] For each PICO question, the certainty of evidence was rated separately for each outcome and then summarized to determine the overall certainty across outcomes. The overall certainty of evidence represented a combined rating across all outcomes considered critical for decision-making, with the lowest certainty of evidence for any critical outcome determining the overall rating. To determine the certainty of evidence for each outcome across all studies, evidence from RCTs was initially rated as "high," followed by assessment of the following five factors that could lead to downgrading: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[3] Risk of bias was assessed using the "Rob 1" Cochrane tool.[10] Inconsistency was evaluated using the Cochrane Q test [with a .10 significance level] and the I^2 statistic [with values >50% indicating significant heterogeneity]. Indirectness was determined according to whether the included studies addressed a population, intervention, or outcome different from that of interest. For continuous outcomes, certainty of evidence was downgraded by one level if the total number of participants was <400 and downgraded by two levels if the number of participants was <100. For dichotomous outcomes, we downgraded one or two levels if the optimal information size was not met and if the 95% CI included important benefits and important harms or very important benefits and very important harms, respectively.

The strength of each recommendation was graded as either "strong," indicating that the desirable effects of an intervention clearly outweigh the undesirable effects [or vice versa], or "weak," indicating greater uncertainty in this balance. The grading also considered the certainty of evidence, patient values and preferences, the balance between benefits and harms, and cost-effectiveness.

During the initial discussions, and based on feedback from previous ECCO guidelines, the group recognized that high-certainty evidence is limited in certain areas of UC management, but clinicians and patients must still make informed decisions. Furthermore, some broad themes related to approaches to care cannot easily be formulated into a PICO question. Applying the GRADE approach in such areas can be resource-intensive and yield recommendations of limited clinical utility. Therefore, a separate series of "practice points"

were developed for these areas of importance. For these, systematic literature review and data extraction were conducted, and the findings were used to inform expert recommendations. The group acknowledges that these practice points are based on a different level of evidence compared with formal GRADE recommendations but considers them to be of practical value to clinicians. These are clearly delineated in the text as distinct from GRADE recommendations.

All recommendations and practice points were subjected to two rounds of online voting by panel members, ECCO National Representatives, and additional reviewers from among ECCO members who applied to the open call but were not selected for the Working Groups [see Acknowledgements]. The pre-final versions of all recommendations and practice points were discussed among panel members during a series of virtual consensus meetings before being put to a vote. Final versions were approved only if at least 80% of panellists agreed with the statement. The resulting statements and draft manuscript were critically reviewed by two external Guideline Committee members and by ECCO Governing Board members, who approved the final version of these guidelines. Statements and practice points are ordered by drug, with those concerning induction and maintenance therapy presented together where relevant. All statements should be read in the context of the supporting text that follows. A concise summary of statements and supporting text is presented at the beginning of each section.

This guideline focuses exclusively on the management of adult patients with UC. For the sake of clarity and brevity, this specification will not be repeated within each individual statement.

The literature search strategies, relevant definitions of patient populations and outcomes, detailed process descriptions, and SoF tables are provided in the Supplementary Material, available as Supplementary Data at *ECCO-JCC* online.

3. General approach to the management of ulcerative colitis

These guidelines present the evidence supporting the use of different medical therapies in the management of UC. They were developed and written based on the available data, which were derived primarily from large-scale RCTs typically comparing an intervention with placebo. Nevertheless, the medical care of a patient with UC extends far beyond the binary choice between a specific drug and no treatment. Furthermore, patients encountered in clinical practice often do not match the profile of those enrolled in clinical trials. It is therefore essential that these guidelines serve to inform physicians about the certainty of evidence underlying each therapeutic option, which must then be interpreted in the context of individual patient characteristics and preferences when formulating a treatment plan.

A key area of ongoing debate concerns the timing of treatment escalation. Evidence for early escalation is less robust in UC than in Crohn's disease [CD]. However, recurrent symptom flares can lead to both physical and psychological harm,[11] as can repeated exposure to corticosteroids.[12] Although the cost of an intervention is considered within the GRADE framework when determining the strength of recommendations, local health-economic factors, which are beyond the scope of these international guidelines, also influence therapeutic decisions. Nonetheless, appropriate and timely identification of patients who may benefit from higher-cost interventions remains essential to achieving optimal health and economic outcomes.[13]

The ultimate goal of UC treatment is to maintain health-related quality of life [QoL] and prevent disability.[14] To achieve this, it is important not only to ensure rapid symptom control but also to achieve endoscopic healing whenever possible, as this is associated with improved long-term outcomes.[15] The expert panel reflected the importance of these endpoints by designating clinical and endoscopic outcomes as being of critical importance in their evaluations.

The term "conventional therapy" has historically been used to distinguish well-established traditional treatments, such as 5-aminosalicylates [5-ASA], corticosteroids, and thiopurine immunomodulators, from biologic agents and other novel targeted small molecules. However, this concept is becoming increasingly outdated, as the costs and accessibility of biologic therapies continue to evolve [particularly with the introduction of biosimilars] and biologic agents are increasingly regarded as a conventional component of UC management. For these guidelines, the consensus group decided to remove from all recommendations the requirement that patients must have failed, proven intolerant to, or have contraindications to "conventional" therapy. However, it should be noted that this generally constitutes a prerequisite for the use of advanced therapies and is included in the approved label in most countries.

Dose escalation has been reported for many of the interventions considered, typically in a non-randomized manner, both among patients experiencing disease flares during RCTs and within cohort studies. Although appropriate dose escalation or optimization can be relevant in clinical practice, the available high-quality trial data in this area remain limited, and uncontrolled studies are prone to multiple potential sources of bias. Therefore, our recommendations are restricted to doses evaluated in RCTs. Beyond the initiation and escalation of medical therapies for UC, determining when and how to reduce or discontinue treatment to minimize risks, costs, and the burden associated with long-term pharmacotherapy represents an important clinical consideration.[16]

Finally, while these guidelines comprehensively evaluate the available evidence for a broad range of therapeutic options used in UC management, it remains the responsibility of local payers to consider the health-economic implications, overall disease burden, and potential long-term outcome impacts of mandating treatment sequences.

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

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

4.1.1. 5-aminosalicylates

Recommendation 1

We recommend oral 5-aminosalicylates to induce remission in patients with mild-to-moderate ulcerative colitis [strong recommendation, low certainty of evidence] [Agreement: 100%]

We performed a meta-analysis of 11 eligible RCTs including a total of 2156 patients evaluated over 4–12 weeks; 5-ASA showed significantly higher efficacy in achieving clinical remission [RR: 1.56; 95% CI: 1.24–1.97] compared with placebo.

Similarly, clinical response in 14 studies [2025 patients in total] evaluated at 2–10 weeks was significantly better for 5-ASA [RR: 1.58; 95% CI: 1.35–1.86], with response observed in 59% of patients receiving 5-ASA compared with 35% of those receiving placebo [SoF Table 1, available as Supplementary Data at *ECCO-JCC* online].

The efficacy of 5-ASA on endoscopic response, evaluated in four RCTs including 416 patients after 4–12 weeks, was greater 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 maximum follow-up of 12 weeks, was 6.1% with 5-ASA versus 9% in the placebo arms [RR: 0.81; 95% CI: 0.47–1.38]. The overall certainty of evidence was rated as low due to significant heterogeneity and potential publication and reporting bias for certain outcomes. However, a strong recommendation is justified by the consistent and clinically relevant benefit of oral 5-ASA over placebo, together with its excellent safety profile, long-standing clinical use, and favorable benefit–risk balance.

A Cochrane meta-analysis confirmed similar efficacy between once-daily and more frequent dosing regimens across multiple studies.[17] This analysis found no apparent differences in outcomes among the various 5-ASA formulations. Despite discussion regarding potential differences in colonic distribution of 5-ASA preparations, no significant differences in outcomes were observed in 5-ASA comparator studies. Therefore, patients with mildly active UC who fail to achieve remission with appropriately dosed oral 5-ASA are unlikely to benefit from switching to an alternative oral 5-ASA formulation.

Recommendation 2

We recommend an oral dose of ≥2 g/day of 5-aminosalicylates to induce clinical remission in patients with mild-to-moderate ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 98%]

A meta-analysis of eight eligible RCTs was performed with a total of 906 patients with mildly-to-moderately active UC treated with different doses of 5-ASA for 6–8 weeks [SoF Table 2, available as Supplementary Data at *ECCO-JCC* online].[18–25] Standard-dose 5-ASA [2–3 g/day] was significantly more effective than low-dose [<2 g/day] in inducing clinical remission [RR: 1.26; 95% CI: 1.07–1.49]. The certainty of evidence was rated as moderate due to a serious risk of bias. No difference between standard and low-dose 5-ASA was found in terms of clinical response [RR: 0.98; 95% CI: 0.71–1.34] in two eligible RCTs.[21,25] In one RCT, 3 g/day of 5-ASA was superior to 1.5 g/day of 5-ASA in inducing endoscopic response [RR: 1.58; 95% CI: 1.29–1.92] and histologic response [RR: 1.34; 95% CI: 1.01–1.78].[22]

In a meta-analysis of 11 eligible RCTs, high-dose 5-ASA [>3 g/day] was comparable with standard-dose [2–3 g/day] 5-ASA in inducing clinical remission [RR: 1.01; 95% CI: 0.87–1.18] after a follow-up of 6–8 weeks.[18–20,22,23,26–31] High-dose 5-ASA was superior to standard-dose 5-ASA in inducing clinical response [RR: 1.21; 95% CI: 1.08–1.36].

With regard to endoscopic response, the meta-analysis of the available data did not demonstrate superiority of the 4.5–4.8 g/day dose compared with 2.4–3 g/day [RR: 0.96; 95% CI: 0.70–1.31][22,30]. Finally, a single study showed a higher rate of endoscopic remission with 5-ASA doses of 4.8 vs 2.4 g/day [RR: 1.19; 95% CI: 1.02–1.39][29] [SoF Table 2, available as Supplementary Data at *ECCO-JCC* online].

No differences between different doses of 5-ASA were observed in adverse events [AEs], SAEs, or drug discontinuation rate due to AEs.

Recommendation 3

We recommend rectal 5-aminosalicylate monotherapy at a dosage of ≥1 g/day for the induction of remission in patients with active proctosigmoiditis [strong recommendation, low certainty of evidence] [Agreement: 98%]

In a meta-analysis with eight studies, the effect of rectal 5-ASA administered at a dosage of ≥1 g per day [range 2–8 weeks] was investigated [SoF Table 3, available as Supplementary Data at *ECCO-JCC* online].[32–39] Although each study mandated endoscopic evidence of rectal inflammation at baseline, they differed in the maximum extent of proximal disease allowed. Compared with placebo, topical 5-ASA treatment resulted in a significantly greater likelihood of achieving clinical remission [RR: 3.56; 95% CI: 2.08–6.09] and clinical response [RR: 2.46; 95% CI: 2.01–3.01]. In the five studies assessing endoscopic response, endoscopic response was also markedly higher in the 5-ASA groups than the placebo groups [RR: 2.75; 95% CI: 2.04–3.7]. The incidence of SAEs did not differ significantly between patients treated with topical 5-ASA and those receiving placebo [RR: 0.26; 95% CI: 0.03–2.29].[32–39] The relevant role of rectal 5-ASA in achieving positive clinical and endoscopic outcomes, as well as the negligible occurrence of SAEs, has been confirmed by two recently published meta-analyses, without significant differences according to dose or formulation.[40,41]

Although the overall certainty of evidence was rated as low, the recommendation supporting topical 5-ASA remains strong due to its well-established clinical effectiveness and excellent safety profile, as demonstrated by extensive real-world use and the consistently low rate of SAEs.

Recommendation 4

We suggest oral 5-aminosalicylates [≥2 g/day] combined with rectal 5-aminosalicylates [≥1 g/day] over oral 5-aminosalicylate monotherapy for induction of remission in patients with active ulcerative colitis with disease extent of proctosigmoiditis or beyond [weak recommendation, very low certainty of evidence] [Agreement: 90%]

Only a few trials 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 4, available as Supplementary Data at *ECCO-JCC* online].[42–45] 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 extent of

proctosigmoiditis or beyond.[42,43] 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.[42–45] These studies included 322 patients and treatment duration was 3–8 weeks. Again, all trials were heterogeneous in terms of patient characteristics, criteria used to define disease activity and remission, doses, and 5-ASA regimens. There was serious inconsistency of 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.[43] 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 certainty of evidence for this outcome was downgraded because of serious indirectness and imprecision.

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.[42] 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 with this very serious imprecision, there was also a serious risk of bias. Therefore, the certainty of the evidence 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 favor of combined therapy in patients for whom combined therapy was acceptable.

4.1.2. Topical corticosteroids

Recommendation 5

We suggest rectal steroids for the induction of remission in patients with mild-to-moderate proctosigmoiditis [weak recommendation, very low certainty of evidence] [Agreement: 100%]

Rectally administered corticosteroids [including budesonide and beclomethasone formulations] are well established in the treatment of proctitis and distal UC and have demonstrated superiority over placebo in multiple domains. Compared with systemic corticosteroids, they provide localized mucosal anti-inflammatory effects with fewer systemic AEs. In a post-hoc analysis of data pooled from phase 2 and phase 3 RCTs of budesonide rectal foam once- or twice-daily or placebo for up to 12 weeks, twice-daily dosing provided significantly higher early response and complete endoscopic remission rates than once-daily or placebo.[46] At week 6, the early response rate was significantly higher in those on twice-daily dosing [45.3%] versus once-daily dosing [32.1%] or placebo [12.8%; $P < .0001$]. A twice-daily regimen may improve early clinical remission, mucosal healing, fecal biomarker normalization, and extend relapse-free intervals.[46] Another study found that a 4-mg budesonide suppository did not differ from 2-mg rectal foam.[47]

Systematic reviews and RCTs support the role of per rectal steroids for the induction of remission in mildly-to-moderately active distal colitis.[48–59] Of five RCTs comparing per rectal steroids with placebo [SoF Table 5, available as Supplementary Data at *ECCO-JCC* online], per rectal steroids were superior in inducing clinical remission [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 were not more frequent [RR: 0.68; 95% CI: 0.10–4.40], though the certainty of evidence for this outcome was very low due to imprecision and indirectness. Given their favorable benefit–risk profile, clinical experience, and low cost, per rectal steroids are suggested for induction of remission in active UC, particularly in patients who do not respond to per rectal 5-ASA.[48]

Recommendation 6

We suggest rectal 5-aminosalicylates over rectal steroids for induction of remission in patients with active proctosigmoiditis [weak recommendation, very low certainty of evidence] [Agreement: 100%]

In treating patients with mildly-to-moderately active distal UC, both per rectal 5-ASA and per rectal corticosteroids, particularly second-generation corticosteroids such as beclomethasone dipropionate and budesonide, have demonstrated efficacy in inducing clinical and endoscopic remission. In the comparison of the two compounds, a meta-analysis of 13 studies involving 1395 adult patients with active distal UC evaluated the comparative efficacy and safety of per rectal 5-ASA at doses of ≥1 g/day versus per rectal corticosteroids [administered as suppositories or enemas] for induction of remission over 2–8 weeks [SoF Table 6, available as Supplementary Data at *ECCO-JCC* online].[35,60–71] Per rectal 5-ASA demonstrated superiority over per rectal steroids for the induction of clinical remission [RR: 1.36; 95% CI: 1.19–1.56]. However, the difference in clinical response rates was not statistically significant [RR: 1.09; 95% CI: 0.97–1.22], indicating comparable effectiveness between both treatments in this outcome domain. Endoscopic response, assessed in five studies that included 376 patients, was similar with either therapy [RR: 1.08; 95% CI: 0.82–1.44].[63,69–72] Furthermore, in nine studies involving 1306 patients, the incidence of SAEs did not differ significantly between groups [RR: 1.21; 95% CI: 0.47–3.08].[62–64,66–70,72] Despite the observed clinical trends, the overall certainty of evidence was rated as very low due to limitations in study design and imprecision.

In clinical practice, treatment with per rectal 5-ASA would be preferable over per rectal corticosteroids given that it can be continued as maintenance therapy and has a favorable long-term safety profile. Per rectal corticosteroids, especially those with lower systemic bioavailability, remain a therapeutic option for induction therapy after failure of per rectal 5-ASA.

Recommendation 7

We suggest not to routinely combine rectal steroids with rectal 5-aminosalicylates in treating mild-to-moderate proctosigmoiditis [weak recommendation, very low certainty of evidence] [Agreement: 100%]

Whilst several studies compared per rectal 5-ASA versus per rectal steroids in adults with mildly-to-moderately active left-sided UC, few studies evaluated combining the two treatments simultaneously. Crispino et al. found that those on combination treatment [5-ASA enema 1.5 g with beclomethasone dipropionate enema 3 mg in 60 mL] given as a single administration over 8 weeks [$n = 40$] had similar outcomes to those on 5-ASA enema alone [4 g in 60 mL, $n = 40$] and beclomethasone enema alone [3 mg in 60 mL, $n = 40$].[73] Although all three arms improved from baseline to week 8, including in the colitis activity index, there were no significant benefits in combining beclomethasone with 5-ASA versus either therapy alone. Mulder et al. compared beclomethasone 3 mg with 5-ASA 2 g and the combination of both compounds in a single enema and found the combination therapy to be superior to either treatment alone without any increase in AEs. The benefits were less marked for those with left-sided colitis versus proctitis.[70]

Although evidence supporting the combination of rectal 5-ASA and corticosteroids is very limited, in practice a short course of dual topical therapy is sometimes used to maximize local treatment before escalation to systemic or immunosuppressive agents or as an adjunct to enhance efficacy alongside systemic therapy. However, the routine combination of rectal steroids with rectal 5-ASA therapy cannot be recommended due to the limited evidence.

4.1.3. Colonic-release corticosteroids

Recommendation 8

We suggest treatment with colonic-release corticosteroids for induction of remission in patients with mild-to-moderate ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 100%]

The effect of treatment with once-daily budesonide multimatrix [MMX] 9 mg for induction of remission in adult patients with mildly-to-moderately active UC has been investigated in three studies [SoF Table 7, available as Supplementary Data at *ECCO-JCC* online].[74–76] A total of 542 patients were included and followed for 8 weeks. Colonic-release corticosteroids were superior to placebo in inducing clinical remission [RR: 2.86; 95% CI: 1.62–5.04] and clinical response [RR: 1.46; 95% CI: 1.11–1.93]. In two studies including 510 patients, endoscopic response was more likely to be achieved with colonic-release corticosteroids compared with placebo [RR: 1.43; 95% CI: 1.10–1.84].[75,76] 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 certainty of evidence for this critical endpoint due to imprecision. Pooled 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].[77] In a subgroup analysis, this benefit was seen in patients with left-sided colitis but not in those with more extensive disease. The most appropriate use of budesonide MMX may be in patients with mildly-to-moderately active disease who do not respond to or are intolerant to optimized 5-ASA therapy. An RCT comparing budesonide MMX 9 mg/day with placebo in patients with active UC despite oral 5-ASA therapy revealed a statistically significant improvement in the combined endpoint of clinical and endoscopic remission [13% vs 7.5%; $P = .049$] and histologic healing [27% vs 17.5%; $P = .016$] in the treatment arm.[78]

Recommendation 9

We suggest against colonic-release steroids over 5-aminosalicylates for the induction of remission in mild-to-moderate ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 98%]

The effect of treatment with once-daily oral budesonide [budesonide and budesonide MMX] versus 5-ASA for induction of remission in adult patients with mildly-to-moderately active UC has been investigated in two studies [SoF Table 8, available as Supplementary Data at *ECCO-JCC* online].[75,79] A total of 300 patients treated with budesonide (9 mg once-daily; conventional budesonide [$n = 177$] and budesonide MMX [$n = 123$]) were compared with 290 patients treated with 5-ASA (3 g [$n = 177$] and 2.4 g [$n = 123$] once-daily) and followed for 8 weeks. In one study, budesonide was not non-inferior to 5-ASA in inducing clinical remission [RR: 0.72; 95% CI: 0.57–0.91].[79] Rates of clinical remission defined as a Clinical Activity Index ≤ 4 were 39.5% with budesonide versus 54.8% with 5-ASA [$P = .52$ for non-inferiority]. In the same study, no difference in induction of endoscopic remission was demonstrated [RR: 0.78; 95% CI: 0.58–1.04]. Moreover, in both studies, the rates of induction of endoscopic response [RR: 1.0; 95% CI: 0.66–1.53] and histologic remission [RR: 0.62; 95% CI: 0.29–1.34] did not differ between budesonide and 5-ASA. Inconsistency and imprecision regarding induction of endoscopic response resulted in a low certainty of evidence for this critical endpoint.

In the two aforementioned studies, the rates of any AEs [RR: 0.94; 95% CI: 0.79–1.12] and SAEs [RR: 0.97; 95% CI: 0.31–3.02] and withdrawal due to AEs [RR: 1.52; 95% CI: 0.78–2.95] did not differ between the two treatment groups.[75,79] The absolute rate of SAEs was low in both groups [approximately 2%]. Very large 95% CIs in SAEs resulted in a low certainty of evidence for this critical endpoint due to imprecision.

Sufficiently meaningful studies are required to draw conclusions about the comparative efficacy and safety of budesonide versus budesonide MMX versus 5-ASA. As long as such studies are not yet available, we suggest not favoring colonic-release steroids over 5-ASA, particularly due to the potential AEs of corticosteroids.

Finally, in a meta-analysis, no differences were found between 5-ASA and beclomethasone dipropionate 5 mg or beclomethasone dipropionate 10 mg or budesonide MMX 9 mg in achieving clinical remission or improvement (OR: 0.90; 95% CI: 0.51–1.57; OR: 1.54; 95% CI: 0.42–5.64; and OR: 1.17;

95% CI: 0.82–1.66).[80] Thus, beclomethasone dipropionate is suggested for the induction of remission in patients with UC in whom 5-ASA therapy has failed or is not tolerated, and who wish to avoid systemic corticosteroids.

4.1.4. Immunomodulators

Recommendation 10

We recommend against the use of thiopurines as monotherapy for the induction of remission in patients with active ulcerative colitis [strong recommendation, very low certainty of evidence] [Agreement: 100%]

Two studies have reported on the use of azathioprine as monotherapy compared with placebo for induction of remission in patients with UC.[81,82] Overall, only 130 patients in two RCTs were analyzed 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 9, available as Supplementary Data at *ECCO-JCC* online]. No placebo-controlled data on clinical response, endoscopic response, or SAEs were available.

The strong recommendation against thiopurine monotherapy for induction is justified by the absence of demonstrated efficacy over placebo, the very slow onset of action, and the availability of clearly more effective induction therapies. The unfavorable benefit–risk balance in the induction setting, together with potential harms and opportunity cost of delaying effective treatment, supports a strong recommendation despite very low certainty of evidence.

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 in whom 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 for the induction of remission across the entire thiopurine class.

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

4.2.1. 5-aminosalycilates

Recommendation 11

We recommend an oral dose of ≥2 g/day of 5-aminosalicylates to maintain remission in patients with mild-to-moderate ulcerative colitis [strong recommendation, very low certainty of evidence] [Agreement: 100%]

We identified two RCTs involving 306 participants with 48–52 weeks of follow-up, which provided evidence relevant to the efficacy of oral 5-ASA to maintain remission in adult patients with mild-to-moderate UC. We synthesized these in a meta-analysis [SoF Table 10, available as Supplementary Data at *ECCO-JCC* online].[83,84] For clinical remission, there was moderate-quality evidence that oral 5-ASA [≥2 g/day] was statistically significantly superior to placebo for maintaining clinical remission [RR: 1.54; 95% CI: 1.11–2.14]. For endoscopic remission, there was moderate-quality evidence favoring the use of 5-ASA, but this did not reach statistical significance [RR: 1.20; 95% CI: 1.00–1.44]. Only one RCT contributed evidence [of very low quality] for SAEs.[84] Treatment with oral 5-ASA [≥2 g/day] was associated with statistically significantly fewer SAEs versus placebo [RR: 0.41; 95% CI: 0.23–0.71].

Although the certainty of evidence was judged to be very low overall [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 observed in referral center-based cohorts.[85]

Recommendation 12

We suggest rectal 5-aminosalicylates monotherapy for the maintenance of remission in patients with proctosigmoiditis [weak recommendation, very low certainty of evidence] [Agreement: 98%]

Four placebo-controlled trials assessed topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis [SoF Table 11, available as Supplementary Data at *ECCO-JCC* online].[86–89] Doses ranged between 1 g three times weekly and 1 g daily, administered as suppositories or enemas over a period of 12–24 months. The choice of rectal formulation [suppository, enema, foam] depended on proximal disease extension.

The use of topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis was significantly superior in maintaining 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, with 5-ASA being superior to placebo [RR: 4.88; 95% CI: 1.31–18.18].[90]

The certainty of evidence was rated as very low due to a serious risk of bias and inconsistency; however, the long clinical experience of efficacy and minimal AEs of rectal formulations of 5-ASA support its use in this setting. These studies did not report data on SAEs; however, 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.[91]

Furthermore, the relevant role of topical 5-ASA in maintaining positive clinical and endoscopic outcomes and the negligible occurrence of SAEs have been confirmed by two recently published meta-analyses, without significant differences according to dose or formulation.[40,41] In any case, for the maintenance of remission in patients with proctosigmoiditis, the decision between oral and topical therapy should be agreed upon with the patient.

Recommendation 13

We suggest discontinuing oral 5-aminosalicylates in patients with active ulcerative colitis initiating advanced therapy [weak recommendation, low certainty of evidence] [Agreement: 82%] **We suggest discontinuing oral 5-aminosalicylates in patients with ulcerative colitis who achieved remission with advanced therapy or immunomodulators** [weak recommendation, low certainty of evidence] [Agreement: 100%]

According to post-hoc analyses of RCT data, the continuation of 5-ASA in patients with UC initiating advanced therapies appears to provide no additional therapeutic benefit [SoF Table 12, available as Supplementary Data at *ECCO-JCC* online].[92–94] Specifically, no advantage was observed in patients starting vedolizumab for induction [RR: 1.02; 95% CI: 0.67–1.55] or maintenance [RR: 1.11; 95% CI: 0.85–1.45] of clinical remission or for induction [RR: 0.87; 95% CI: 0.57–1.33] or maintenance [RR: 0.94; 95% CI: 0.72–1.22] of endoscopic remission.[92] Similarly, pooled analyses of infliximab and golimumab trials demonstrated no added efficacy from continuing 5-ASA for induction or maintenance of either clinical remission [RR: 0.90; 95% CI: 0.80–1.02 and RR: 0.91; 95% CI: 0.71–1.18, respectively] or endoscopic remission [RR: 0.88; 95% CI: 0.75–1.05 and RR: 0.97; 95% CI: 0.85–1.11, respectively].[93] Comparable findings were reported for ustekinumab, adalimumab, and tofacitinib [RR: 1.07; 95% CI: 0.90–1.27; RR: 0.98; 95% CI: 0.36–2.7, and RR: 0.70; 95% CI: 0.28–1.75, respectively], with no safety differences observed.[92–94]

In patients already receiving advanced therapy or immunomodulators, discontinuation of 5-ASA also appears safe. In a large real-world analysis including 3589 patients with UC from the United States Truven MarketScan and Danish national databases, stopping 5-ASA after initiating anti-tumor necrosis factor [anti-TNF] therapy was not associated with an increased risk of adverse outcomes.[95] No advantage was seen with ustekinumab[96] and findings for tofacitinib were inconsistent; a Japanese cohort suggested reduced relapse risk with 5 mg twice-daily tofacitinib plus 5-ASA but not with 10 mg twice-daily.[97] Data on concomitant 5-ASA with thiopurines remain limited and do not indicate a clear clinical benefit.[98]

Although continuation of 5-ASA does not appear to affect efficacy or safety in the setting of advanced therapies, other considerations, such as treatment cost[99] and its debated chemopreventive role,[100–102] may influence clinical decisions. Thus, in selected high-risk subgroups, including patients with primary sclerosing cholangitis or a family history of colorectal cancer, continued 5-ASA use may remain appropriate.

4.2.2. Immunomodulators

Recommendation 14

We suggest monotherapy with thiopurines for the maintenance of remission in patients under 65 years of age with steroid-dependent ulcerative colitis or who are intolerant to 5-aminosalicylates [weak recommendation, low certainty of evidence] [Agreement: 98%]

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 13, available as Supplementary Data at *ECCO-JCC* online].[81,82,103,104] In 232 patients followed for 1 year, azathioprine was superior to placebo 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 RCTs, 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 have highlighted the apparent clinical benefit of thiopurine monotherapy.[105] 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.

Significant safety concerns do exist with the use of thiopurines. This is particularly true in patients aged >65 years; use of thiopurines should be discouraged in this age group.[106–109]

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

5.1. Systemic corticosteroids

Recommendation 15

We recommend short-term oral prednisolone for induction of remission in non-hospitalized patients with moderate-to-severe ulcerative colitis [strong recommendation, very low certainty of evidence] [Agreement: 100%]

The use of systemic corticosteroids for the induction of remission in moderately-to-severely active UC is well established in clinical practice, despite a limited evidence base. This is due in part to the large effect size and limited alternative options available at the time of the original RCTs.[110,111] A previous meta-analysis included five placebo-controlled RCTs,[112] although only two of them used systemic corticosteroids.[110,111] Therefore, we performed a meta-analysis of just these two studies and calculated an RR of 2.83 [95% CI: 1.79–4.46] for the induction of clinical remission [SoF Table 14, available as Supplementary data at *ECCO-JCC* online].[110,111] The certainty

of evidence was rated as very low, due to a serious risk of bias, indirectness, and imprecision, in part due to the low number of patients included in each study. However, a strong recommendation is justified by the large and clinically important effect of systemic corticosteroids on induction of remission, their rapid onset of action, their acceptable benefit–risk balance when used for a short duration, and the extensive clinical experience in moderate-to-severe UC. No information regarding AEs with steroid treatment was available in these two studies.[110,111] Other studies have established the side-effect profile of corticosteroids for both short-term and longer-term exposure in both UC and CD.[12,113] Corticosteroid-free remission represents a desired outcome for patients.[114,115]

5-ASA therapy has demonstrated efficacy for induction of moderately active but not for severely active UC. A meta-analysis by Feagan et al. showed that patients with moderately active UC benefited from treatment with 5-ASA at 2.4 g daily, whereas corticosteroid therapy was more effective for patients with severe UC.[116] Extensive experience with systemic steroids in clinical practice and the favorable balance between their potential benefit and harm [when used over limited periods] supports the recommendation for oral systemic steroids [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.

Although the optimal dose and regimen for systemic corticosteroids in UC is uncertain, a 40 mg/day dose is typically used and this recommendation is based on an outpatient study where 40 mg/day was more effective than 20 mg/day.[117] There is no evidence of benefit with doses >40–60 mg/day, and doses >40 mg/day may be associated with increased AEs.[112,117] Single-daily dosing is as effective as split dosing and causes less adrenal suppression.[118] It is essential to administer corticosteroids only for short-term use. The dose should typically be tapered over 6–8 weeks.[119,120]

A previous 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.[112] However, none of these RCTs used a colonic-release budesonide formulation. We restrict our recommendations for budesonide MMX in mildly-to-moderately active disease and prednisolone in moderately-to-severely active UC to reflect the study populations of the RCTs identified and the probable risk–benefit profile in these distinct populations.

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

5.2. Anti-tumour necrosis factor agents

5.2.1. Anti-tumor necrosis factor agents for the induction of remission

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 15, available as Supplementary data at *ECCO-JCC* online].[121–128]

Recommendation 16

We recommend treatment with anti-tumor necrosis factor agents [infliximab, adalimumab, and golimumab] for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 98%]

Patient eligibility required an inadequate response with or intolerance to conventional therapies, which were defined as corticosteroids, immunomodulators, or both in most studies, although three RCTs also permitted inadequate response with or intolerance to oral 5-ASA alone.[121–123]

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 [critical outcome] used in this guideline [endoscopic response]; evidence was therefore downgraded due to indirectness. There was no difference in AEs when analysed regardless of treatment duration [RR: 0.84; 95% CI: 0.64–1.09]. Safety data for anti-TNF agents from large cohort studies were generally reassuring.[108,109,129] RCTs that directly compared different anti-TNF agents were not available.

Recommendation 17

We suggest that either infliximab monotherapy or infliximab in combination with a thiopurine can be used for the induction of remission in patients with moderate-to-severe ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 95%]

There are limited studies that have compared infliximab monotherapy with infliximab combination therapy with a thiopurine in the setting of UC. One RCT compared outcomes in patients receiving infliximab versus a combination of infliximab and azathioprine [SoF Table 16, available as Supplementary data at *ECCO-JCC* online].[130] The primary endpoint was corticosteroid-free clinical remission at week 16, which was higher in infliximab combination therapy with azathioprine versus infliximab monotherapy [RR: 1.80; 95% CI: 1.09–2.97]. However, there was no statistically significant difference for clinical response [RR: 0.97; 95% CI: 0.86–1.10], endoscopic response [RR: 1.15; 95% CI: 0.88–1.50], any AEs [RR: 1.13; 95% CI: 0.74–1.72], discontinuation due to an AE [RR: 1.46; 95% CI: 0.25–8.52], or SAEs [RR: 6.83; 95% CI: 0.36–130.04].

Potential benefits of combination therapy [infliximab and a thiopurine] include decreased risks of immunogenicity, increased

durability of treatment, and increased treatment efficacy. However, monotherapy [infliximab without a thiopurine] has been proposed in some instances to reduce potential risks of combination therapy, including higher risk of AEs, greater medication burden for patients, and potentially higher direct healthcare costs.

Recommendation 18

We suggest adalimumab monotherapy for induction of remission in patients with moderate-to-severe ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 98%]

Comparative data on adalimumab monotherapy versus adalimumab combined with a thiopurine in UC are limited. One RCT of adalimumab performed a subgroup analysis comparing outcomes in patients receiving adalimumab versus a combination of adalimumab and a thiopurine immunomodulator [SoF Table 17, available as Supplementary data at *ECCO-JCC* online].[126] The primary endpoint was clinical remission at week 8. Based on this subgroup analysis, there was no significant difference between the two groups.

Currently, there are insufficient data to suggest using an immunomodulator in combination with adalimumab for the induction of remission in patients with moderate-to-severe UC. Given the potentially higher risk of AEs with combination therapy with an immunomodulator, there may be a preference among clinicians and patients to use adalimumab monotherapy.

Finally, evidence from an RCT involving 98 patients [50 with UC] suggested that combination therapy was associated with fewer treatment failures and a lower likelihood of anti-drug antibody development when a second anti-TNF agent was introduced.[131] However, outcomes for the UC subgroup were not reported, and the small sample size further limits the certainty of these findings.

5.2.2. Anti-tumor necrosis factor agents for the maintenance of remission

Recommendation 19

We recommend anti-tumor necrosis factor agents [infliximab, adalimumab, and golimumab] for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with the same drug [strong recommendation, high certainty of evidence] [Agreement: 100%]

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 18, available as Supplementary data at *ECCO-JCC* online].[121–128,132,133] 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], sustained clinical remission [RR: 2.76; 95% CI: 1.78–4.28], and improvement in QoL [RR: 1.71; 95% CI: 1.27–2.32]. 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; however, data were insufficient.

Large-scale cohort studies support the safety of these drugs.[108,109,129] Recent evidence has shown that the subcutaneous formulation of infliximab [CT-P13] provides comparable efficacy and safety to intravenous [IV] administration in patients with UC.[134,135]

Recommendation 20

We suggest either infliximab monotherapy or infliximab in combination with a thiopurine for the maintenance of remission in patients with moderate-to-severe ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 100%]

There are limited data comparing infliximab monotherapy with infliximab combination therapy with a thiopurine for the maintenance of remission in patients with UC [SoF Table 19, available as Supplementary data at *ECCO-JCC* online][136]. A post-hoc subgroup analysis from the ACT-1 and ACT-2 trials compared outcomes for patients who received infliximab with or without an immunomodulator.[130] No significant difference was noted between either treatment arm for clinical remission [RR: 1.13; 95% CI: 0.79–1.61] or clinical response [RR: 1.01; 95% CI: 0.84–1.21]. However, infliximab monotherapy [without a thiopurine] has been advocated in certain contexts to mitigate the potential risks associated with combination therapy, including a higher incidence of AEs, increased treatment burden for patients, and potentially greater direct healthcare expenditures.

An RCT of 98 patients [50 with UC] suggested lower rates of treatment failure and reduced development of anti-drug antibodies with combination therapy in the case of a second anti-TNF agent being used.[131] However, this trial did not examine outcomes for the subgroup of patients with UC, which, alongside the small number of patients in this trial, suggests that these findings should be interpreted with caution.

It has been hypothesized that subcutaneous infliximab may provide more stable, steady-state drug concentrations and therefore potentially avoid the need for combination therapy with a thiopurine. A post-hoc exploratory analysis including 237 patients from the LIBERTY-UC study [monotherapy, $n = 180$; combination therapy, $n = 57$] demonstrated similar clinical outcomes [clinical remission, clinical response, corticosteroid-free remission, and endoscopic–histologic mucosal improvement] at week 54 and week 102 between patients in both groups.[137]

Recommendation 21

No recommendation for clinical practice can be made between adalimumab monotherapy or adalimumab in combination with a thiopurine for the maintenance of remission in patients with moderate-to-severe ulcerative colitis [no recommendation, no evidence] [Agreement: 89%]

There was an absence of data comparing adalimumab monotherapy with adalimumab combination therapy with a thiopurine specifically for maintenance of remission in UC. Potential advantages attributed to combining adalimumab with a thiopurine include reduced immunogenicity, greater long-term maintenance of therapy, and enhanced therapeutic

effectiveness. Conversely, adalimumab monotherapy has been promoted in certain settings to avoid drawbacks associated with combination regimens, including a higher likelihood of AEs, increased patient treatment burden, and the possibility of increased direct healthcare expenditures.

5.3. Vedolizumab

5.3.1. Vedolizumab for the induction of remission

Recommendation 22

We recommend treatment with vedolizumab for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, low certainty of evidence] [Agreement: 100%]

Two placebo-controlled RCTs were identified that addressed our PICO question. These included 620 patients with moderately-to-severely active UC in adult patients treated with vedolizumab or placebo. Patients were followed up for 6–10 weeks. Induction of clinical remission, induction of clinical response, and SAEs were reported [SoF Table 20, available as Supplementary data at *ECCO-JCC* online].[138,139] We included these two studies in a meta-analysis. Clinical remission was observed more often in patients initiating vedolizumab compared with placebo [RR: 2.14; 95% CI: 1.03–4.43]. The direction of effect for clinical response was similar, although the difference compared with placebo was not statistically significant, with a borderline lower limit of the 95% CI [RR: 1.51; 95% CI: 0.99–3.39]. Evidence was also sought for endoscopic remission, defined as a Mayo endoscopic subscore of either 0 or 1 in both trials. In GEMINI 1, vedolizumab-treated patients reached endoscopic remission more often than placebo-treated patients at week 6 [40.9% vs 24.8%; $P = .001$].[138,139]

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 favorable safety assessment.[129] Data were also examined for other safety endpoints during induction only, such as the number of patients experiencing any AEs [GEMINI 1: 90/225 for vedolizumab vs 69/149 for placebo; Japanese phase 3 trial: 82/164 for vedolizumab vs 43/82 for placebo] and the number of patients with AEs leading to treatment discontinuation [Japanese phase 3 trial: 8/164 for vedolizumab vs 2/82 for placebo],[138] confirming the reassuring safety profile of vedolizumab.

The overall certainty of evidence was low due to serious inconsistency and imprecision for clinical remission, yet the recommendation was graded as strong, considering the favorable balance between efficacy and safety data.

5.3.2. Vedolizumab for the maintenance of remission

Recommendation 23

We recommend vedolizumab for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with vedolizumab [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

We identified three RCTs that included 441 patients treated with IV vedolizumab or placebo, which 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 21, available as Supplementary data at *ECCO-JCC* online].[138–141] Patients in these trials were followed up for 52–60 weeks. We performed a meta-analysis of results from these trials. Induction responders who subsequently received vedolizumab were more likely to achieve clinical remission than those receiving placebo after 52–60 weeks of follow-up [RR: 2.37; 95% CI: 1.74–3.23]. Continued vedolizumab therapy also conferred significant benefits over placebo in terms of steroid-free clinical remission, sustained clinical remission, endoscopic remission, and improvements in QoL. More recently, subcutaneous vedolizumab was approved for maintenance treatment in UC; this indication is supported by the efficacy and safety findings from the VISIBLE program.[140]

The meta-analysis pooled rates of SAEs in patients treated with vedolizumab to either induce or maintain remission and found no difference compared with placebo [RR: 0.71; 95% CI: 0.39–1.30].[138–140] Data were also examined for other safety endpoints during maintenance only, such as the [pooled] number of patients experiencing any AEs [177/217 for vedolizumab vs 182/224 for placebo; data from three trials][138–140] and the [pooled] number of patients with AEs leading to treatment discontinuation [4/95 for vedolizumab vs 11/98 for placebo; data from two trials],[139,140] confirming the reassuring safety profile of vedolizumab.

The overall certainty of evidence was moderate due to serious imprecision arising from sparse data, yet the recommendation was graded as strong, reflecting the overall favorable appraisal of the efficacy–safety profile.

5.3.3. Vedolizumab versus adalimumab for the induction and maintenance of remission

Recommendation 24

We suggest the use of vedolizumab rather than adalimumab for the induction and maintenance of remission in moderate-to-severe ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 100%]

The preference of vedolizumab over adalimumab in patients with moderate-to-severe UC is supported by VARSITY, an RCT that compared the efficacy and safety of IV vedolizumab and adalimumab in 769 patients with moderately-to-severely active UC [SoF Table 22, available as Supplementary data at *ECCO-JCC* online].[142] Vedolizumab demonstrated significantly superior rates of clinical response at the end of induction [RR: 1.46; 95% CI: 1.29–1.67], clinical remission [RR: 1.39; 95% CI: 1.10–1.76], endoscopic remission [RR: 1.43; 95% CI: 1.17–1.75], and QoL improvement at week 52 [RR: 1.23; 95% CI: 1.06–1.43] when compared with adalimumab. In the subgroup analysis, the results were statistically significant in biologic-naive patients and only numerically superior in the biologic-exposed population. Although steroid-free clinical remission was numerically lower in the vedolizumab group than in the adalimumab group [RR: 0.58; 95% CI: 0.32–1.05], the certainty of evidence was low as the analysis relied on

sparse data and the CIs were very wide. The incidence of SAEs was similar between the two groups [RR: 0.80; 95% CI: 0.55–1.17].

Post-hoc analyses of VARSITY also demonstrated greater early disease control,[143] improved QoL,[143] and greater histologic remission and minimal histologic disease activity at week 14 and 52 with vedolizumab compared with adalimumab.[144]

However, the VARSITY trial did not allow for dose escalation in either group, which may have limited its findings. Additionally, a post-hoc analysis of VARSITY, which validated a clinical decision support tool developed for vedolizumab in UC, showed that most VARSITY trial patients included in the analysis had a high baseline predicted probability of response to vedolizumab, and vedolizumab was superior to adalimumab only in these patients.[145] Interestingly, this high-probability group included both anti-TNF-naive and anti-TNF-experienced patients. In this way, the clinical decision support tool could be used in either subgroup to estimate the likelihood of response to vedolizumab, potentially guiding treatment selection between vedolizumab and adalimumab in clinical practice. Other factors should also inform therapeutic decisions, such as the presence of extraintestinal manifestations. In this context, adalimumab may be preferred as it offers a systemic anti-inflammatory effect, in contrast to the gut-selective mechanism of vedolizumab.[146]

5.4. Ustekinumab

5.4.1. Ustekinumab for the induction of remission

Recommendation 25

We recommend treatment with ustekinumab for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

A single RCT compared ustekinumab with placebo for induction therapy in adult patients with moderately-to-severely active UC [SoF Table 23, available as Supplementary data at *ECCO-JCC* online].[147] Patients were required to have not responded to or been intolerant to previous biologic or conventional therapy [defined as corticosteroid or thiopurines] or both or have corticosteroid-dependent disease. Of these, 51.6% of randomized patients had previously failed treatment with an alternative biologic, including 18% 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 [RR: 2.91; 95% CI: 1.72–4.94], clinical response [RR: 1.97; 95% CI: 1.64–2.37], and endoscopic improvement [RR: 1.96; 95% CI: 1.41–2.72].

At completion of induction, the change in mean Inflammatory Bowel Disease Questionnaire [IBDQ] score from baseline was greater in those receiving ustekinumab than in those receiving placebo [35.0 vs 16.16; $P < .001$]. Median change in fecal calprotectin from baseline also showed a more significant reduction in the ustekinumab arm [–1368 vs 17.9 µg/g; $P < .001$].

SAEs did not differ between ustekinumab and placebo [RR: 0.67; 95% CI: 0.39–1.17].

5.4.2. Ustekinumab for the maintenance of remission

Recommendation 26

We recommend ustekinumab for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with ustekinumab [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

A single RCT compared ustekinumab with placebo for maintenance therapy in UC in adult patients who responded to ustekinumab induction therapy [SoF Table 24, available as Supplementary data at *ECCO-JCC* online].[147] The study revealed that maintenance treatment with ustekinumab at the approved dosing of 90 mg SC 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 remission, we used data for the closely related endpoint of endoscopic improvement and found benefit compared with placebo [RR: 1.79; 95% CI: 1.36–2.36]. There was a reduction in mean fecal calprotectin for those who remained on ustekinumab during the maintenance period [–435 vs 813 µg/g]. 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 [RR: 0.67; 95% CI: 0.39–1.17].

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 previous biologic failure.

5.5. Interleukin-23 inhibitors

5.5.1. Mirikizumab

5.5.1.1. Mirikizumab for the induction of remission

Recommendation 27

We recommend treatment with mirikizumab for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

Two RCTs evaluated the efficacy of mirikizumab for the induction of remission in adult patients with UC [SoF Table 25, available as Supplementary data at *ECCO-JCC* online].[148,149] The first was a phase 2 RCT in which 249 patients with moderate-to-severe UC were randomized to receive one of three IV doses of mirikizumab [50, 200, or 600 mg administered at weeks 0, 4, and 8] or placebo. The primary endpoint was clinical remission at week 12.[149] The second was a phase 3 RCT

in which 1162 patients with moderate-to-severe UC were randomized to receive mirikizumab 300 mg IV or placebo at weeks 0, 4, and 8. The primary endpoint was clinical remission at week 12.[148] Included patients had an inadequate response, loss of response, or were intolerant to corticosteroids, immunomodulators, biologic therapies, or tofacitinib.

We included both studies in a meta-analysis. At week 12, clinical response and clinical remission were achieved significantly more often in patients receiving mirikizumab compared with placebo [RR: 1.79; 95% CI: 1.14–2.83 and RR: 1.98; 95% CI: 1.29–3.06, respectively]. Endoscopic response and endoscopic remission were also more frequent with mirikizumab than placebo [RR: 3.56; 95% CI: 1.33–9.52 and RR: 1.72; 95% CI: 1.36–2.18, respectively]. However, the certainty of evidence for endoscopic response was downgraded due to imprecision, as the optimal information size was not met.[149] A greater proportion of patients in the mirikizumab group achieved histologic remission compared with placebo [RR: 1.85; 95% CI: 1.44–2.39].[149,150] Bowel urgency improvement and remission were achieved more frequently with mirikizumab than with placebo [RR: 1.51; 95% CI: 1.26–1.82 and RR: 1.87; 95% CI: 1.40–2.51, respectively].[151] Health-related QoL, as assessed using IBDQ scores, also improved more often with mirikizumab than with placebo [RR: 1.30; 95% CI: 1.17–1.45 for response and RR: 1.44; 95% CI: 1.24–1.68 for remission].[148]

The rates of SAEs and AEs leading to treatment discontinuation were significantly lower in patients treated with mirikizumab than in those receiving placebo [RR: 0.56; 95% CI: 0.32–0.98 and RR: 0.23; 95% CI: 0.13–0.42, respectively].[148,149]

5.5.1.2. Mirikizumab for the maintenance of remission

Recommendation 28

We recommend mirikizumab for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with mirikizumab [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

One RCT was identified that evaluated mirikizumab for the maintenance of remission in adult patients with UC [SoF Table 26, available as Supplementary data at *ECCO-JCC* online].[148] In this phase 3 study, 544 patients who had responded to induction therapy with mirikizumab at week 12 were re-randomized to receive either SC mirikizumab 200 mg or placebo every 4 weeks. The primary endpoint was clinical remission at week 52. When compared with placebo, a significantly higher proportion of patients treated with mirikizumab achieved clinical remission [RR: 1.98; 95% CI: 1.51–2.61], endoscopic remission [RR: 2.01; 95% CI: 1.57–2.56], and histologic remission [RR: 1.97; 95% CI: 1.49–2.60][150] at week 52. Notably, a higher proportion of patients in the mirikizumab group also achieved steroid-free clinical remission and sustained clinical remission [RR: 2.06; 95% CI: 1.53–2.78 and RR: 1.72; 95% CI: 1.23–2.42, respectively].

Rates of SAEs and AEs leading to treatment discontinuation were significantly lower with mirikizumab than with placebo [RR: 0.43; 95% CI: 0.21–0.88 and RR: 0.19; 95% CI: 0.07–0.47, respectively]. However, the certainty of evidence for all these endpoints was downgraded due to imprecision, as the optimal information size was not met.

In addition, a randomized phase 2 study that had demonstrated the superiority of mirikizumab over placebo during the induction phase included a maintenance phase.[149] In this trial, 93 patients who responded to mirikizumab at week 12 were re-randomized to receive SC mirikizumab 200 mg either every 4 weeks or every 12 weeks through week 52. At week 52, clinical remission was achieved in 46.8% of patients receiving mirikizumab every 4 weeks and in 37.0% of those receiving mirikizumab every 12 weeks, indicating sustained efficacy throughout the maintenance period.[149]

5.5.2. Risankizumab

5.5.2.1. Risankizumab for the induction of remission

Recommendation 29

We recommend treatment with risankizumab for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

A single RCT compared risankizumab with placebo for induction therapy in adult patients with moderately-to-severely active UC [SoF Table 27, available as Supplementary data at *ECCO-JCC* online].[152] In the induction trial, patients were randomized to receive 1200 mg of risankizumab [$n = 650$; 51.2% had inadequate response to advanced therapy and 48.8% had inadequate response to non-advanced therapy] or placebo [$n = 325$] both administered IV at weeks 0, 4, and 8. At week 12, risankizumab significantly improved clinical remission rates compared with placebo (20.3% vs 6.2%, respectively; adjusted between-group difference [BGD]: 14.0% [95% CI: 10.0–18.0%]; $P < .001$). The occurrence of UC-related hospitalizations was significantly reduced in the risankizumab group compared with the placebo group through week 12 (0.8% vs 5.5%, respectively; BGD: −4.8% [95% CI: −7.3% to −2.2%]; $P < .001$).

In terms of secondary outcomes, compared with placebo risankizumab significantly improved clinical response (64.3% vs 35.7%, respectively, BGD: 28.6% [95% CI: 22.3–34.8%]; $P < .001$), endoscopic improvement (36.5% vs 12.1%, BGD: 24.3% [95% CI: 19.3–29.4%]; $P < .001$), endoscopic remission (10.6% vs 3.4%, BGD: 7.2% [95% CI: 4.2–10.2%]; $P < .001$), histological, endoscopic, and mucosal improvement (24.5% vs 7.7%, BGD: 16.6% [95% CI: 12.3–21.0%]; $P < .001$), and histological, endoscopic, and mucosal remission (6.3% vs 0.6%, BGD: 5.6% [95% CI: 3.5–7.7%]; $P < .001$). Compared with placebo, risankizumab significantly improved the patient-reported outcomes of absence of bowel urgency [$P < .001$], absence of abdominal pain [$P = .002$], absence of nocturnal bowel movements [$P < .001$], absence of tenesmus [$P < .001$], fecal incontinence [$P < .001$], sleep interruption [$P < .001$], fatigue [$P < .001$], and health-related QoL [$P < .001$].

The most frequently reported AEs in the induction trial were COVID-19 [4.8%] and anemia [3.4%] in the risankizumab group. The most frequent AEs in the placebo group were active

UC [10.2%] and anemia [6.5%]. The rate of SAEs was 2.3% for risankizumab compared with 10.2% for placebo. One treatment-emergent death occurred in the risankizumab group and was due to respiratory failure caused by COVID-19 pneumonia.

5.5.2.2. Risankizumab for the maintenance of remission

Recommendation 30

We recommend risankizumab for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with risankizumab [strong recommendation, low certainty of evidence] [Agreement: 100%]

Patients eligible for the maintenance trial had been enrolled in the induction trial and had an adequate response to risankizumab at 12- or 24-week follow-up. In the maintenance trial, each dose of risankizumab significantly improved clinical remission rates compared with placebo (40.2% for 180 mg risankizumab and 37.6% for 360 mg risankizumab vs 25.1% for placebo, BGD for 180 mg risankizumab vs placebo: 16.3% [95% CI: 6.1–26.6%]; $P < .001$) [SoF Table 28, available as Supplementary data at *ECCO-JCC* online].[152]

In terms of secondary outcomes, each dose of risankizumab significantly improved clinical response (68.2% for 180 mg risankizumab [$P < .001$] and 62.3% for 360 mg risankizumab [$P = .02$] vs 51.9% for placebo), endoscopic improvement (50.8% for 180 mg risankizumab [$P < .001$] and 48.3% for 360 mg risankizumab [$P < .001$] vs 31.7% for placebo), endoscopic remission (23.2% for 180 mg risankizumab [$P = .01$] and 24.3% for 360 mg risankizumab [$P = .01$] vs 14.8% for placebo), histological, endoscopic, and mucosal improvement (42.8% for 180 mg risankizumab [$P < .001$] and 42.2% for 360 mg risankizumab [$P < .001$] vs 23.5% for placebo), and corticosteroid-free remission (39.0% for 180 mg risankizumab [$P < .01$] and 37.1% for 360 mg risankizumab [$P < .01$] vs 25.1% for placebo).[152] No significant differences between each dose of risankizumab and placebo were observed for histological, endoscopic, or mucosal remission.[152]

In the maintenance trial, the most frequently reported AEs among all treatment groups were active UC [13.0% in the 180 mg risankizumab group and 13.8% in the 360 mg risankizumab group vs 14.8% in the placebo group] and COVID-19 [8.8% in the 180 mg risankizumab group and 13.3% in the 360 mg risankizumab group vs 11.7% for placebo]. SAEs were reported in 5.2% in the 180 mg risankizumab group and 5.1% in the 360 mg risankizumab group versus 8.2% in the placebo group.[152]

A strong recommendation is justified by the consistent and clinically meaningful benefit of risankizumab over placebo across multiple maintenance outcomes, including clinical, endoscopic, and corticosteroid-free remission in patients who responded to induction therapy. Within the GRADE framework, the clear favorable benefit–risk balance supports a strong recommendation despite low certainty of evidence driven mainly by imprecision.

5.5.3. Guselkumab

5.5.3.1. Guselkumab for the induction of remission

Recommendation 31

We recommend treatment with guselkumab for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

The following placebo-controlled RCTs were identified that assessed the efficacy of guselkumab for inducing remission in adult patients with moderately-to-severely active UC: QUASAR phases 2b and 3 [SoF Table 29, available as Supplementary data at *ECCO-JCC* online].[153,154] Both studies were included in our meta-analysis and enrolled 907 patients treated with guselkumab 200 mg or placebo. Mean duration of follow-up was 12 weeks. Guselkumab 200 mg was superior to placebo in achieving a clinical response [RR: 2.21; 95% CI: 1.86–2.64], clinical remission [RR: 2.82; 95% CI: 1.95–4.08], endoscopic response [RR: 2.44; 95% CI: 1.79–3.33], and endoscopic remission at week 12 [RR: 2.89; 95% CI: 1.82–4.59].

One trial included 212 patients treated with guselkumab 400 mg or placebo.[153] Similarly, guselkumab 400 mg was superior to placebo in achieving a clinical response [RR: 2.20; 95% CI: 1.56–3.11], clinical remission [RR: 2.65; 95% CI: 1.35–5.20], endoscopic response [RR: 2.49; 95% CI: 1.39–4.46], and endoscopic remission at week 12 [RR: 2.10; 95% CI: 0.89–4.95].[153]

Both doses of guselkumab [200 and 400 mg] were superior to placebo in achieving histologic response and improving IBDQ and PROMIS-Fatigue SF7 scores. SC guselkumab is also effective for induction of remission in UC; this indication is supported by the efficacy and safety results from the ASTRO program.[155]

Patients experienced fewer SAEs with guselkumab 200 mg [RR: 0.37; 95% CI: 0.19–0.71] and 400 mg [RR: 0.49; 95% CI: 0.13–1.91] than with placebo.[153,154]

5.5.3.2. Guselkumab for the maintenance of remission

Recommendation 32

We recommend guselkumab for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with guselkumab [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

A single RCT compared guselkumab 100 or 200 mg with placebo for maintenance of remission in adult patients with UC who responded to induction with guselkumab [SoF Table 30, available as Supplementary data at *ECCO-JCC* online].[154] Duration of follow-up was 44 weeks. A total of 378 patients received either guselkumab 100 mg or placebo, while 380 patients received either guselkumab 200 mg or placebo.

Guselkumab 100 mg was superior to placebo in achieving a clinical response [RR: 1.80; 95% CI: 1.50–2.15], clinical remission [RR: 2.39; 95% CI: 1.71–3.33], steroid-free remission [RR: 2.45; 95% CI: 1.75–3.44], endoscopic response [RR:

2.61; 95% CI: 1.88–3.62], and endoscopic remission at week 44 [RR: 2.27; 95% CI: 1.54–3.34].[154]

Guselkumab 200 mg was superior to placebo in achieving a clinical response [RR: 1.73; 95% CI: 1.44–2.08], clinical remission [RR: 2.79; 95% CI: 2.01–3.85], steroid-free remission [RR: 2.66; 95% CI: 1.91–3.71], endoscopic response [RR: 2.72; 95% CI: 1.97–3.77], and endoscopic remission at week 44 [RR: 2.21; 95% CI: 1.49–3.26].[154]

Both doses of guselkumab [100 and 200 mg] were superior to placebo in achieving sustained clinical remission, histologic healing, and improvements in IBDQ and PROMIS-Fatigue SF7 scores.

Patients experienced more SAEs with guselkumab 100 mg [RR: 5.16; 95% CI: 0.61–43.76] and 200 mg [RR: 12.13; 95% CI: 1.59–92.34] than with placebo.[154] However, the overall incidence of SAEs was low across all groups.

5.6. Janus kinase inhibitors

5.6.1. Tofacitinib

5.6.1.1. Tofacitinib for the induction of remission

Recommendation 33

We recommend treatment with tofacitinib for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

We performed a meta-analysis of data from two RCTs relevant to our PICO question. These included 1220 adult patients with moderate-to-severe UC who previously had an inadequate response, loss of response, or were intolerant to either conventional therapy [5-ASA plus steroids or thiopurines] or a biologic agent and who were treated with tofacitinib or placebo [SoF Table 31, available as Supplementary data at *ECCO-JCC* online].[156,157] 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 due to the low number of events. Tofacitinib had broadly similar differences in induction of clinical and endoscopic outcomes compared with placebo in patients with previous anti-TNF agent exposure, although the absolute remission rates achieved were lower. The use of an extended induction period [using induction dosing at 10 mg twice-daily orally] is worth considering for delayed responders.

SAEs were comparable in the tofacitinib and placebo groups [RR: 0.70; 95% CI: 0.45–1.08], although the evidence was also downgraded due to imprecision.

5.6.1.2. Tofacitinib for the maintenance of remission

Recommendation 34

We recommend tofacitinib for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with tofacitinib [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

A single RCT reported outcomes in 593 adult patients with moderate-to-severe UC who responded to induction treatment with tofacitinib and were treated with tofacitinib or placebo as maintenance therapy [SoF Table 32, available as Supplementary data at *ECCO-JCC* online].[157] 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]. However, the evidence regarding endoscopic remission was downgraded due to imprecision resulting from the 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 likewise downgraded due to imprecision.

Dose de-escalation in maintenance treatment with tofacitinib is desirable. A recent RCT of dose de-escalation [RIVETING] from tofacitinib 10 mg twice-daily to 5 mg twice-daily compared with continued maintenance with 10 mg twice-daily in patients in stable remission showed high rates of sustained remission with dose de-escalation [77% vs 90%].[158] The study demonstrated that subjects who had achieved a baseline Mayo endoscopy subscore of 0 and those without prior anti-TNF failure were more likely to maintain remission. These results are consistent with a large multicenter real-world cohort study of 334 patients with UC [UC-REMIT] treated with tofacitinib, which demonstrated that patients with severe disease [Mayo endoscopy subscore = 3] and those with prior biologic failure were at higher risk of losing response after dose reduction.[159]

SAEs for tofacitinib therapy in the OCTAVE RCTs were comparable with placebo [RR: 0.70; 95% CI: 0.45–1.08], although the evidence was downgraded due to imprecision. However, an increased risk of infections was observed [OR: 1.56; 95% CI: 1.18–2.06]. The most serious infections were of bacterial origin, including community-acquired pneumonia and urinary tract and skin infections. Long-term extension safety data in patients with UC undergoing follow-up for up to 9.2 years of exposure have reported overall low rates of AEs of special interest other than herpes zoster [3.24 events/100 person-years of exposure] and serious infections [1.8 events/100 person-years of exposure].[160] Rates of herpes zoster were noted to increase with age and most cases were not deemed serious. Lower rates of herpes zoster infection [0.5 events/100 person-years of exposure] have been reported in real-world studies of tofacitinib use in a patient cohort with high rates of herpes zoster vaccination.[159] A systematic review has demonstrated that risks of herpes zoster are dose-related for both tofacitinib and upadacitinib, underscoring the importance of dose de-escalation where possible.[161]

A safety study of tofacitinib in patients aged ≥50 years with rheumatoid arthritis and with at least one known cardiovascular risk factor revealed hazard ratios—when compared with anti-TNF treatment—of 1.33 [95% CI: 0.91–1.94] for cardiovascular events and 1.48 [95% CI: 1.04–2.09] for cancers, and non-inferiority of tofacitinib was not demonstrated based on the prespecified limits.[162] The European Medicines Agency subsequently issued additional guidance for risk minimization for Janus kinase inhibitors [JAKi], including tofacitinib.[163] The measures specified that JAKi should be used only if no suitable treatment alternatives are available in those aged ≥65 years and

those with cardiovascular risk factors. They also recommended using JAKi with caution in patients with risk factors for venous thromboembolism. A separate meta-analysis of the safety profile of JAKi across multiple inflammatory diseases did not demonstrate high rates of major adverse cardiovascular events [0.48 events/100 person-years of exposure],[164] and no increased risk was observed in patients aged <65 years who have never smoked.[165]

5.6.2. Filgotinib

5.6.2.1. Filgotinib for the induction of remission

Recommendation 35

We recommend treatment with filgotinib for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 98%]

A total of two RCTs were identified to address this PICO [SoF Table 33, available as Supplementary data at *ECCO-JCC* online].[166] The SELECTION trials, which were phase 2b/3 randomized, placebo-controlled trials, evaluated filgotinib in the following two parallel induction studies: Study A [biologic-naive] and Study B [biologic-experienced].[166] Both filgotinib 100 and 200 mg were assessed against placebo over a 10-week induction period. Filgotinib 200 mg demonstrated statistically significant efficacy over placebo in achieving multiple clinically relevant endpoints, namely clinical remission [RR: 1.88; 95% CI: 1.27–2.80], endoscopic remission [RR: 2.63; 95% CI: 1.24–5.56], histologic remission [RR: 1.53; 95% CI: 1.07–2.18], and endoscopic improvement [RR: 1.82; 95% CI: 1.32–2.51]. There were consistent improvements across QoL measures, including both the physical and mental components of the SF-36 and the IBDQ scores. Additionally, work productivity loss, as measured by the Work Productivity and Activity Impairment, was reduced by a mean difference of –13.42 [95% CI: –19.4 to –7.45]. Certainty of evidence was rated as moderate for clinical efficacy outcomes due to imprecision [optimal information size not met]. The incidence of any AEs, discontinuation due to AEs, and SAEs were comparable with placebo. No clinically relevant safety signals were identified.

Filgotinib 100 mg was associated with numerically improved outcomes, but the effects were less pronounced and more uncertain than those observed with the 200-mg dose. While some outcomes were promising, the overall clinical benefit of 100 mg was limited by wide CIs and failure to meet significance thresholds in key remission outcomes.

5.6.2.2. Filgotinib for the maintenance of remission

Recommendation 36

We recommend filgotinib for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with filgotinib [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

In the SELECTION phase 2b/3 trial, filgotinib 200 mg demonstrated significant efficacy in maintaining clinical remission through 58 weeks compared with placebo, with a clinical remission rate of 37.2% at week 58 versus 11.2% for placebo [difference: 26.0%; 95% CI: 16.0–35.9; $P < .0001$] [SoF Table 34, available as Supplementary data at *ECCO-JCC* online].[166] Long-term extension data further support sustained remission, with up to 80% of patients in partial Mayo Clinic Score remission at 144 weeks among long-term completers. The safety profile was acceptable, with no new safety signals identified over approximately 4 years of follow-up.[167]

Filgotinib 100 mg once-daily may be considered for maintenance of remission in adult patients with moderately-to-severely active UC who have responded to induction therapy, particularly in cases where the 200-mg dose is not appropriate [eg, specific regulatory or demographic restrictions]. In the SELECTION trial, filgotinib 100 mg achieved a clinical remission rate of 23.8% at week 58 compared with 13.5% for placebo [difference: 10.4%; 95% CI: 0.0–20.7; $P = .0420$].[166] While effective, the 100-mg dose was less efficacious than the 200-mg dose for both induction and maintenance of remission.[166,168] Long-term extension data confirm continued benefit, though remission rates were numerically lower than with 200 mg.[167]

Exposure-adjusted incidence rates for serious infection, thromboembolic events, and major adverse cardiovascular events were consistently low across patient groups during maintenance treatment. Most patients with major adverse cardiovascular events had cardiovascular risk factors. The exposure-adjusted incidence rate for herpes zoster was numerically higher for filgotinib 200 mg than for placebo. Most herpes zoster cases were mild-to-moderate [grade 2 or lower], with only one grade 3 event reported.

5.6.3. Upadacitinib

5.6.3.1. Upadacitinib for the induction of remission

Recommendation 37

We recommend treatment with upadacitinib for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

Three RCTs [one phase 2b study and two replicate phase 3 induction trials, U-ACHIEVE and U-ACCOMPLISH] evaluated upadacitinib in 1090 adult patients with moderate-to-severe UC who had previously experienced an inadequate response, loss of response, or intolerance to at least one oral 5-ASA, corticosteroid, immunosuppressant, or biological therapy [infliximab, adalimumab, golimumab, vedolizumab, or ustekinumab] [SoF Table 35, available as Supplementary data at *ECCO-JCC* online].[169] We conducted a meta-analysis of data from these three RCTs, which demonstrated a significant benefit of upadacitinib 45 mg once-daily over placebo at the end of the 8-week induction phase for multiple outcomes, including clinical remission [RR: 7.15; 95% CI: 4.26–11.99], clinical response [RR: 2.85; 95% CI: 2.38–3.42], endoscopic response [RR: 5.53; 95% CI: 3.78–8.09], and endoscopic remission [RR:

11.06; 95% CI: 4.75–25.76].[169] Similarly, a significantly higher proportion of patients treated with upadacitinib achieved mucosal healing than those receiving placebo [$P < .00001$]. The certainty of evidence for this outcome, as well as for clinical remission and endoscopic response and remission, was downgraded due to imprecision. A positive impact was also observed on QoL improvement, with 79.9% of patients achieving an IBDQ response [≥16-point increase from baseline] versus 42.8% with placebo [RR: 1.86; 95% CI: 1.64–2.10]. Additionally, more patients reported absence of urgency [RR: 2.33; 95% CI: 1.73–3.15].[169–172]

The risk of any AEs was similar between groups [RR: 1.02; 95% CI: 0.78–1.35], as was the incidence of serious AEs [RR: 0.55; 95% CI: 0.30–0.98].[169,170] However, the certainty of evidence for these outcomes was downgraded due to imprecision and inconsistency.

In the aforementioned RCTs, patients with an incomplete response after 8 weeks of treatment with upadacitinib 45 mg once-daily were offered an additional 8 weeks of open-label induction, after which 48.3% achieved a clinical response at week 16. Of these patients, 26.5% and 43.6% achieved clinical remission at week 52 with upadacitinib 15 and 30 mg, respectively.[173] These findings suggest that, in selected cases, extending induction to 16 weeks may be beneficial and improve outcomes.

5.6.3.2. Upadacitinib for the maintenance of remission

Recommendation 38

We recommend upadacitinib for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with upadacitinib [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

Clinical responders from the induction upadacitinib RCTs were re-randomized [1:1:1] to receive once-daily upadacitinib 15 mg [$n = 148$], upadacitinib 30 mg [$n = 154$], or placebo [$n = 149$] [SoF Table 36, available as Supplementary data at *ECCO-JCC* online].[169] Compared with placebo, maintenance therapy with upadacitinib 15 and 30 mg resulted in significantly higher rates of clinical remission [42.6% with 15 mg and 51.9% with 30 mg vs 12.1% with placebo, respectively; $P < .00001$ for both comparisons], steroid-free clinical remission [57.4% and 67.2% vs 22.2%; $P < .0008$ and $P < .0001$, respectively], endoscopic response [48.6% and 61.7% vs 14.8%, respectively; $P < .00001$ for both], and endoscopic remission [24.3% and 26.0% vs 5.4%, respectively; $P < .0001$ for both] at week 52.[169] A significantly greater proportion of patients receiving maintenance upadacitinib also achieved mucosal healing [$P < .001$ for 15 mg; $P < .0006$ for 30 mg vs placebo], absence of urgency [$P < .00001$ for both doses], and improved QoL [$P < .00001$ for both doses] as measured by the IBDQ.[171] However, the certainty of evidence for all these outcomes was downgraded due to imprecision [optimal information size not met].

The overall incidence of any AEs and SAEs was similar across treatment groups [15 mg vs placebo and 30 mg vs placebo] with the exception of the rate of SAEs, which was significantly higher in patients receiving placebo, with 12.8% [19/149 patients] experiencing an SAE compared with 5.8% [9/154 patients] in the upadacitinib 30 mg group [$P < .04$]. Apart from UC worsening, the most frequently reported AEs were nasopharyngitis, elevated creatine phosphokinase, arthralgia, and upper respiratory tract infections. Herpes zoster was observed in patients receiving upadacitinib 15 mg [4%] and 30 mg [4%]; herpes zoster was not observed in the placebo group.[169] The certainty of evidence was rated as high for any AEs, but downgraded for SAEs due to imprecision.

5.7. Sphingosine 1-phosphate receptor modulators

5.7.1. Ozanimod

5.7.1.1. Ozanimod for the induction of remission

Recommendation 39

We recommend treatment with ozanimod for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

Two RCTs evaluated the efficacy and safety of ozanimod for induction therapy in adult patients with moderately-to-severely active UC [SoF Table 37, available as Supplementary data at *ECCO-JCC* online].[174,175] The first trial assessed both ozanimod 0.5 and 1 mg versus placebo, while the second [the True North Study] focused on ozanimod 1 mg. The 1-mg dose of ozanimod demonstrated statistically and clinically significant improvements across multiple outcomes. Clinical response [RR: 1.75; 95% CI: 1.42–2.15] and remission [RR: 2.97; 95% CI: 1.80–4.90] were both superior to placebo. Endoscopic response [RR: 2.36; 95% CI: 1.58–3.51], mucosal healing [RR: 3.08; 95% CI: 1.84–5.15], and histologic remission [RR: 2.08; 95% CI: 0.91–4.77] also favored ozanimod, although some outcomes were downgraded for imprecision, resulting in moderate quality. Safety outcomes showed no significant increase in AEs, with moderate-to-low quality due to wide CIs and low event rates.

For ozanimod 0.5 mg, the effect sizes were smaller and less consistent.

These findings support the use of the 1-mg dose for induction in clinical practice.

5.7.1.2. Ozanimod for the maintenance of remission

Recommendation 40

We recommend ozanimod for the maintenance of remission in patients with ulcerative colitis who responded to induction therapy with ozanimod [strong recommendation, moderate certainty of evidence] [Agreement: 100%]

The same two RCTs evaluated the efficacy and safety of ozanimod at doses of 0.5 and 1 mg compared with placebo in adult patients with moderately-to-severely active UC who had responded to induction therapy [SoF Table 38, available as Supplementary data at *ECCO-JCC* online].[174,175] Ozanimod 1 mg demonstrated superior efficacy over placebo in maintaining

clinical response [RR: 1.48; 95% CI: 1.25–1.76], clinical remission [RR: 2.01; 95% CI: 1.48–2.72], steroid-free remission [RR: 1.90; 95% CI: 1.34–2.68], and mucosal healing [RR: 1.97; 95% CI: 1.42–2.72], all with moderate certainty of evidence. Additionally, ozanimod 1 mg significantly improved histologic remission [RR: 2.50; 95% CI: 1.08–5.79]. In biologic-exposed patients, a numerical benefit of ozanimod over placebo was observed but did not reach statistical significance, probably due to smaller sample size and lower overall response rates.

Safety outcomes, including rates of SAEs and discontinuations due to AEs, were comparable or even slightly better than placebo, with a low incidence of treatment-limiting AEs.

5.7.2. Etrasimod

5.7.2.1. Etrasimod for the induction of remission

Recommendation 41

We recommend treatment with etrasimod for the induction of remission in moderate-to-severe ulcerative colitis [strong recommendation, low certainty of evidence] [Agreement: 98%]

One phase 2 RCT and two phase 3 RCTs [ELEVATE UC 12 and ELEVATE UC 52] were conducted, including 847 adult patients with moderately-to-severely active UC who had failed at least one approved UC therapy. A significant benefit was observed after 12 weeks of treatment with etrasimod 2 mg once-daily compared with placebo in clinical response [RR: 1.64; 95% CI: 1.39–1.93], remission [RR: 2.72; 95% CI: 1.42–5.21], and endoscopic response [RR: 2.05; 95% CI: 1.55–2.71] [SoF Table 39, available as Supplementary data at *ECCO-JCC* online].[176,177] Additionally, endoscopic remission rates in the phase 3 RCTs, including patients with isolated proctitis, were significantly higher in the etrasimod group.[176] Etrasimod also demonstrated clinically meaningful improvements across multiple health-related QoL measures.[178] Etrasimod led to a greater proportion of patients achieving symptomatic remission compared with placebo by week 2 in ELEVATE UC 52 and by week 4 in ELEVATE UC 12.[176] More stringent efficacy outcomes, such as histologic improvement and remission, were also more frequently observed among patients receiving etrasimod at week 12 [RR: 3.11; 95% CI: 1.21–7.99 and RR: 2.39; 95% CI: 1.20–4.75, respectively].[177–179] When stratified by previous treatment, clinical response, remission, and endoscopic improvement were more frequently observed among etrasimod-treated patients naive to biologics or JAKi, while only ELEVATE UC 52 showed statistically significant benefits in etrasimod-treated patients previously treated with biologics or JAKi.[176–180]

The overall safety profile of 12-week etrasimod therapy was favorable, with no differences in any AE or SAE rates compared with placebo, but with higher rates of AEs leading to treatment discontinuation.[176,177] There were isolated cases of bradyarrhythmias [mostly asymptomatic], occurring mainly during the initial days of treatment and resolving without specific intervention.[176] The overall certainty of evidence supporting this statement was rated as low due to the sparse data on SAEs. Nevertheless, given that the certainty of evidence for other critical outcomes was assessed as moderate to high, we issued a strong recommendation for the use of etrasimod as induction therapy in patients with moderate-to-severe UC.

5.7.2.2. Etrasimod for the maintenance of remission

Recommendation 42

We recommend etrasimod for the maintenance of remission in patients with moderate-to-severe ulcerative colitis who responded to induction therapy with etrasimod [strong recommendation, low certainty of evidence] [Agreement: 100%]

The efficacy and safety of once-daily etrasimod 2 mg as maintenance therapy in adult patients with moderately-to-severely active UC for up to 52 weeks were assessed in a single phase 3 RCT [ELEVATE UC 52] [SoF Table 40, available as Supplementary data at *ECCO-JCC* online].[176] The probability of achieving clinical and steroid-free clinical remission [defined as clinical remission at week 52 without steroid use for ≥12 weeks before week 52] was significantly higher in the etrasimod group compared with placebo [RR: 4.82; 95% CI: 2.50–9.27 and RR: 4.82; 95% CI: 2.50–9.27, respectively]. Additionally, various domains of health-related QoL were meaningfully improved by the end of maintenance treatment.[178] Histologic and endoscopic remission rates were significantly higher among individuals receiving etrasimod [RR: 2.18; 95% CI: 1.38–3.43 and RR: 4.43; 95% CI: 2.20–8.94, respectively].[179] Although clinical and steroid-free clinical remission rates were numerically lower among patients previously treated with biologics or JAKi, differences versus placebo remained statistically significant.[176,180]

Therapy with etrasimod for 52 weeks was generally safe. Most AEs were mild to moderate.[176] There were no differences in SAEs or AEs leading to treatment discontinuation between groups; however, the RR for any AEs was slightly higher in the etrasimod group [RR: 1.27; 95% CI: 1.08–1.49]. The most frequent AEs were anemia, headache, and worsening of UC. In the etrasimod group, the incidence of macular edema was low and comparable with placebo. No increased infection risk or malignancies were reported in etrasimod trials.[176] The overall certainty of evidence supporting this statement was judged to be low, largely because of limitations in the data on SAEs and AEs leading to treatment discontinuation. However, given that the evidence for other critical outcomes was graded as moderate to high, we made a strong recommendation for the use of etrasimod as maintenance therapy in patients with moderate-to-severe UC.

6. Medical management of acute severe ulcerative colitis

6.1. Intravenous corticosteroids

Recommendation 43

We recommend intravenous corticosteroids as first-line therapy to induce clinical remission in hospitalized patients with acute severe ulcerative colitis [strong recommendation, low certainty of evidence] [Agreement: 100%]

The sole placebo-controlled RCT in acute severe UC [ASUC] remains the landmark study by Truelove and Witts.[181] In 210 hospitalized adults, IV cortisone [approximately 100 mg/day] induced clinical remission in 41% versus 16% with placebo at 6 weeks [RR: 2.61; 95% CI: 1.58–4.31]. Endoscopic

remission—normal or near-normal mucosa on sigmoidoscopy—was likewise superior with steroids [30% vs 11%; RR: 2.87; 95% CI: 1.23–6.67]. Although the reduction in surgery did not reach significance [8% vs 15%; RR: 0.56; 95% CI: 0.25–1.21], early mortality was halved [4.6% vs 10.9%]. Rates of perforation, massive hemorrhage, and other SAEs were similar between arms, confirming an acceptable short-term safety profile.[181] Given the clear benefit demonstrated and the ethical constraints of withholding corticosteroids, further placebo-controlled trials are neither feasible nor justifiable. Subsequent observational studies and contemporary clinical practice uniformly corroborate the pivotal role of IV corticosteroids as initial therapy in ASUC. Within the GRADE framework, the magnitude of effect, life-saving potential, ethical impossibility of further placebo-controlled trials, and extensive corroborating clinical experience support a strong recommendation despite low certainty of evidence.

6.2. Addition of 5-aminosalicylates to intravenous corticosteroids

Recommendation 44

We suggest against the addition of oral 5-aminosalicylates to intravenous corticosteroids in hospitalized patients with acute severe ulcerative colitis [weak recommendation, low certainty of evidence] [Agreement: 100%]

A single RCT evaluated the question of whether to start or continue treatment with 5-ASA in patients hospitalized for ASUC treated with IV corticosteroids [SoF Table 41, available as Supplementary data at *ECCO-JCC* online].[182] In this study, 149 patients with ASUC were randomized to receive either corticosteroids with 4 g of oral 5-ASA or corticosteroids alone. The combination of 5-ASA and steroids did not result in improved outcomes, namely clinical response at day 7 [RR: 0.95; 95% CI: 0.79–1.15], need for salvage therapy with cyclosporine or infliximab at day 7 [RR: 1.04; 95% CI: 0.48–2.25], or need for surgery at 7 days or 1 month [RR: 1.56; 95% CI: 0.27–9.08] or 3 months [RR: 0.99; 95% CI: 0.21–4.72]. There were also no differences in the occurrence of any AEs [RR: 0.50; 95% CI: 0.09–2.65]. There was an exploratory signal of reduced need for biologics by day 90 in patients who continued 5-ASA after hospitalization, which warrants further research on this topic.

The certainty of evidence was only moderate for clinical response at day 7, as optimal information size was not met, and low for the other outcomes due to very large CIs. Given the low certainty of evidence and potential risk of AEs with 5-ASA [albeit low], a weak recommendation against the addition of oral 5-ASA to IV steroids is provided.

6.3. Maintenance therapy after response to intravenous corticosteroids

Practice point 1

In patients with acute severe ulcerative colitis who respond to intravenous corticosteroids, we suggest against maintenance with only thiopurines or 5-aminosalicylates [Agreement: 95%]

IV corticosteroids are universally recommended as first-line therapy for ASUC. Nevertheless, only about 60%–70% of patients with ASUC achieve an adequate short-term response to IV corticosteroids alone, underscoring the high risk of early relapse and colectomy.[183] Evidence guiding maintenance therapy in responders is therefore limited. Observational data are inconsistent. Maintenance with 5-ASA after an IV-corticosteroid response is sub-optimal, as more than half of patients relapse within 12 months.[104] In a single-center cohort with 46-month follow-up, relapse rates were comparable when maintenance therapy was 5-ASA, thiopurines, or anti-TNF, suggesting no clear benefit for any option.[184] By contrast, a larger multicenter study showed a significantly lower relapse risk with anti-TNF agents, suggesting a potential advantage over conventional drugs.[185]

Recently, the multicenter ACTIVE trial addressed this gap by randomizing thiopurine- and biologic-naive adults who had responded to IV corticosteroids for ASUC to receive either infliximab plus azathioprine or azathioprine monotherapy for 52 weeks.[186] IV corticosteroids were stopped within 7 days in the infliximab plus azathioprine arm, whereas the azathioprine monotherapy arm used a prolonged taper starting at 1 mg/kg/day for 3 weeks followed by weekly dose reductions. In the intention-to-treat analysis [$n = 64$], treatment failure [a composite of steroid-free clinical remission loss, lack of endoscopic response, need for rescue therapy, SAEs, colectomy, or death] occurred in 53% of the infliximab plus azathioprine arm versus 82% of the azathioprine arm [RR: 3.85; 95% CI: 1.15–12.9].[186] Steroid-free clinical remission at week 52 was achieved in 52% with combination therapy versus 22% with azathioprine alone [$P = .02$], with no signal of excess serious infections or deaths in either arm. However, key limitations temper these findings; the study was open-label; recruitment stopped early due to the COVID-19 pandemic, yielding a smaller sample than planned; and the composite primary endpoint may overestimate clinical benefit. Moreover, other advanced biologics or small-molecule agents were not compared.

Taken together, the ACTIVE trial provides the first high-quality evidence favoring infliximab plus azathioprine as maintenance therapy after an ASUC flare responsive to IV corticosteroids, showing clinically meaningful reductions in treatment failure without new safety concerns. However, careful safety assessment is warranted. To minimize infection risk from triple immunosuppression, standard infection monitoring and a rapid steroid taper—within 7 days, as applied in the ACTIVE trial—should be considered. Moreover, in the ACTIVE trial, the infliximab plus azathioprine combination was maintained throughout the 52-week follow-up; no controlled data exist beyond 1 year, and continuation of combination therapy thereafter should be individualized according to clinical response, safety, and patient risk profile. In summary, pending confirmatory data, it seems that combination therapy with infliximab plus azathioprine should be considered the preferred option in this setting.

Data on vedolizumab or ustekinumab are limited to small, retrospective "bridge" cohorts initiated after induction with calcineurin inhibitors or anti-TNF agents, and no RCTs have evaluated them as maintenance therapy following an IV steroid response.[187] The TACOS RCT tested high-dose tofacitinib plus IV steroids only during the acute phase and used different maintenance regimens for responders and thus

cannot clarify benefit after a steroid response.[188] Finally, a small, uncontrolled series with upadacitinib plus IV steroids likewise lacked comparator data and used supra-label doses.[189] No controlled trials have evaluated JAKi specifically as maintenance after IV corticosteroid response. Given the limited evidence available, comparative data for other advanced agents [vedolizumab, ustekinumab, JAKi] in this specific post-IV corticosteroid response setting are scarce; these options may be considered on a case-by-case basis. Head-to-head RCTs with these agents are needed to define optimal therapeutic choice.

6.4. Infliximab versus cyclosporine

Recommendation 45

We recommend either cyclosporine or infliximab as rescue therapy in patients with steroid-refractory acute severe ulcerative colitis [strong recommendation, high certainty of evidence] [Agreement: 100%]

Two RCTs have compared infliximab and cyclosporine as rescue therapies for patients with ASUC refractory to IV corticosteroids. The first study by Laharie et al.[190] enrolled 115 patients [58 receiving infliximab and 57 receiving cyclosporine] across 30 centers in France refractory to 0.8 mg/kg/day of methylprednisolone or equivalent for at least 5 days. Colectomy rates at day 98 were 17% in the infliximab group versus 21% in the cyclosporine group; the differences were not statistically significant. Endoscopic remission at day 98 [defined by an endoscopic Mayo score of 0 or 1] was similar in both groups [45%, infliximab group vs 47%, cyclosporine group; $P = .85$]. SAEs were comparable [25%, infliximab group vs 16%, cyclosporine group].

The CONSTRUCT trial was an open-label trial conducted in the UK across 52 centers with 270 patients randomized [135 per group].[191] The primary outcome was quality-adjusted survival, calculated as the area under the curve [AUC] of EuroQol 5-Dimension scores. No significant difference was observed [AUC 564, infliximab group vs 587, cyclosporine group; $P = .603$]. Colectomy rates were 30.9% and 34.9% in the infliximab group versus 29.1% and 38.5% in the cyclosporine group at 1 and 5 years, respectively [$P = .97$]. SAEs occurred in 16% [infliximab] and 19% [cyclosporine].

A more recent subanalysis of the CYSIF trial focused on endoscopic outcomes.[192] Among 55 patients [infliximab group, $n = 29$; cyclosporine group, $n = 26$], endoscopic remission at day 98 [Ulcerative Colitis Endoscopic Index of Severity of 0] was significantly more frequent with infliximab [73% vs 25%; $P < .001$]. Data on long-term colectomy and patient-reported outcomes were not reported in this analysis.

In summary, the available evidence supports the use of either infliximab or cyclosporine as rescue therapy in ASUC refractory to IV corticosteroids, with comparable colectomy rates, safety profiles, and QoL outcomes across trials. However, infliximab was associated with significantly greater short-term endoscopic remission.

6.5. Dose and intervals of infliximab

Recommendation 46

There is insufficient evidence for the routine use of infliximab at higher doses or at dosing intervals shorter than standard induction dosing in acute severe ulcerative colitis; however, individualized dosing approaches can be considered [weak recommendation, very low certainty of evidence] [Agreement: 90%]

Only one RCT [PREDICT-UC] was identified that compared the application of intensified initial rescue [infliximab 10 mg/kg] versus standard initial rescue [infliximab 5 mg/kg] dose therapy in patients with steroid-refractory ASUC [$n = 138$] [SoF Table 42, available as Supplementary data at *ECCO-JCC* online].[193] After this first dose, there was no significant difference in the primary outcome—clinical response by day 7—between both groups [65% vs 61%; $P = .62$]. Post-hoc analysis indicated that a numerically higher proportion of patients with hypoalbuminemia and high C-reactive protein levels had a clinical response by day 7 if they received 10 mg/kg versus 5 mg/kg as a first dose.

Patients in the 10 mg/kg group received a second dose at day 7 or earlier at the time of non-response, while patients in the 5 mg/kg group were re-randomized at day 3–7 to a standard induction strategy [5 mg/kg infliximab at weeks 0, 2, and 6, with an extra 5 mg/kg dose between days 3 and 7 if no response] or an accelerated induction strategy [5 mg/kg infliximab at weeks 0, 1, and 3, with the week-1 dose increased to 10 mg/kg and given between days 3 and 7 if no response]. There was also no significant difference in clinical response by day 14 or in clinical, endoscopic, or steroid-free remission or colectomy rates by month 3 in this comparison of intensified versus accelerated induction strategy.

However, post-hoc analysis indicated that among patients who received an initial 5 mg/kg dose, response rates were numerically lower in patients with lower albumin levels and those with a high C-reactive protein.[193] This may suggest that patients with a higher inflammatory burden, higher clearance, or both may benefit from a higher initial infliximab dose, as infliximab clearance is a major determinant of outcomes in ASUC. Further exploratory studies of PREDICT-UC demonstrated that early infliximab levels and clearance could predict outcomes in ASUC, and that a high early infliximab clearance can be overcome by additional dosing.[194] Lower serum infliximab levels at day 3 [≤57.9 µg/mL] were associated with a higher risk of induction failure at day 14 and colectomy at month 3, indicating the potential need for early intensive re-dosing of infliximab.[194] Further studies are required to determine the potential benefit of accelerated or high-dose infliximab rescue therapy in patients based on their individual drug clearance.

The overall recommendation was graded as weak, due to the existence of only one RCT, in which randomization was not based on drug clearance. The certainty of evidence was judged to be very low due to high risk of detection bias and imprecision.

6.4. Treatments other than infliximab or cyclosporine

Practice point 2

We suggest considering the use of Janus kinase inhibitors as rescue therapy in hospitalized patients with steroid-refractory acute severe ulcerative colitis who have failed or cannot receive infliximab or cyclosporine after careful risk assessment and consideration of surgical options. Due to the limited available data, the use of ustekinumab or vedolizumab as a standalone induction agent in the setting of acute severe ulcerative colitis cannot be recommended [Agreement: 98%]

Among the most promising alternatives to infliximab and calcineurin inhibitors in ASUC are JAKi[195]. Some of the potential advantages of JAKi are rapid absorption and clearance and lack of effect on plasma albumin levels, which may hamper the effectiveness of monoclonal antibodies.[187] A systematic review of tofacitinib in ASUC included 148 patients and revealed colectomy-free survival of 85% at 30 days, 86% at 90 days, and 69% at 180 days. Clinical remission ranged from 35% to 69% and endoscopic remission reached 55%.[196] The GETAID multicenter cohort of 55 patients reported colectomy-free survival of 78.9% and 73.6% at 3 and 6 months, respectively.[197] AEs occurred in 22 patients, predominantly infectious complications other than herpes zoster [$n = 13$], and resulted in tofacitinib discontinuation in seven patients.

The only currently published RCT [TACOS trial] demonstrated superior clinical response [83.0% vs 58.8%; $P = .007$] of tofacitinib as an add-on to IV corticosteroids compared with IV corticosteroids alone and reduced need for rescue therapy [13% vs 38% at day 90; $P = .003$]. One patient in the tofacitinib arm and three patients in the placebo arm died.[188] Some of the studies, including the prospective TACOS study, used higher induction doses such as 10 mg/8 h;[188,198,199] the only available study to compare a 10 mg twice-daily dose to a 10 mg three times daily dose suggested superior efficacy of the higher dose.[200]

Data on the use of upadacitinib in the ASUC setting are currently sparse. In the systematic review by Damianos et al., 55 patients with ASUC treated with upadacitinib from 11 case series were reviewed.[201] The pooled 90-day colectomy-free survival rate was 83.7%; among those who avoided colectomy, 80% achieved steroid-free clinical remission. Most patients received the standard induction dose of 45 mg daily. Two venous thromboembolic events were reported, but no treatment-related deaths occurred.

Although JAKi show promising short-term efficacy in ASUC, several important limitations and knowledge gaps remain. Current evidence is derived primarily from observational studies and a single RCT [TACOS], with no head-to-head comparisons against standard rescue therapies such as infliximab or cyclosporine. The optimal dosing strategy, particularly regarding high-intensity induction regimens, remains uncertain. Moreover, safety signals, such as infectious complications and thromboembolic events, require further clarification. Data on upadacitinib are even more limited, originating exclusively from retrospective case series with no prospective validation.

Vedolizumab was evaluated in several case series for ASUC, the largest including 71 patients.[187,202] In all studies, vedolizumab was combined with a calcineurin inhibitor, either in parallel or as an add-on. In a recent systematic review summarizing eight studies with 156 patients, the overall rate of colectomy avoidance was 69%.[187] In the largest of the studies evaluating combined therapy with vedolizumab and calcineurin inhibitors, colectomy-free survival rates were 93% at 3 months, 67% at 1 year, and 55% at 2 years.[202]

For ustekinumab, the evidence supporting its use in ASUC is even more limited. The largest retrospective series included 10[203] and 12[204] biologic-experienced patients, in all of whom induction with a calcineurin inhibitor was introduced. In the GETAID study, all 10 patients avoided colectomy at 6 months;[203] in the German study, 9/11 patients avoided colectomy at 3–6 months.[204] As both vedolizumab and ustekinumab were used within the framework of a calcineurin induction strategy, it is not possible to address relevant safety considerations.

6.5. Rescue therapy after cyclosporine or infliximab failure

Recommendation 47

We suggest that the use of a third-line sequential rescue therapy with infliximab, a calcineurin inhibitor, or a Janus kinase inhibitor may be considered in highly selected patients with acute severe ulcerative colitis who are refractory to intravenous corticosteroids and a second-line treatment [infliximab or calcineurin inhibitor] in experienced multidisciplinary centers and after discussion of surgical options and potential risks and benefits [weak recommendation, low certainty of evidence] [Agreement: 100%]

In patients with ASUC who failed to respond to IV corticosteroids and an additional line of rescue therapy [calcineurin inhibitor or infliximab], the main therapeutic options generally include colectomy or a trial of an additional treatment line. While a medical option may delay or defer colectomy in a proportion of patients, significant risks from profound immunosuppression and the potential risk of toxic megacolon and colonic perforation, which may be increased by delaying surgery, should be considered. To date, the main therapeutic third-line options may include one of the three following sequences: cyclosporine followed by infliximab, infliximab followed by cyclosporine, or JAKi [upadacitinib or tofacitinib] following failure of either previous agent. In a recent systematic review that included 23 studies, third-line rescue therapy resulted in avoidance of colectomy in 53% of patients with ASUC [95% CI: 47%–58%].[187] In an earlier meta-analysis of 10 studies, 62% and 39% of patients achieved short-term treatment response and remission, respectively, with colectomy rates of 28% and 42% at 3 and 12 months, respectively.[205] Importantly, a pooled 26% rate of AEs and a mortality rate of 0.88% were calculated.[187] In the recent REASUC study, 78 patients with ASUC on third-line therapy were included; 32 received infliximab and 46 received cyclosporine as second-line rescue treatment. Third-line treatment was infliximab in 45 [58%], cyclosporine in 17 [22%], tofacitinib in 13 [17%], and ustekinumab in three [3.8%] patients. Colectomy was required

in 29 patients [37%] during follow-up [median 21 weeks]; 32 and 18 patients were in clinical remission at 12 and 52 weeks, respectively. AEs were reported in 26 [33%] patients, including two deaths [2.6%].[206]

The evidence on the effectiveness of JAKi for treatment of ASUC is rapidly accumulating; in a recent systematic review of 11 studies including a total of 55 patients with ASUC treated with upadacitinib [most patients were biologic-experienced], colectomy was avoided in 83.7%.[201] A systematic review including 21 studies with 148 patients [the largest including 55 patients from the GETAID cohort][197] treated with tofacitinib for ASUC reported 85% colectomy avoidance at 30 days.[196] However, the number of patients reported as having received JAKi as rescue therapy after failing either cyclosporine or infliximab during the same hospitalization is currently very limited.

At this point, due to limited and heterogeneous data, it is not possible to compare the effectiveness and safety across these therapeutic scenarios. Some considerations for selecting a strategy may include local expertise and availability, specific safety considerations, previous treatment response history, and pharmacokinetics or pharmacodynamics. Importantly, while cyclosporine and JAKi are short-acting agents with limited half-life, infliximab is associated with a prolonged duration of immunosuppression that may be associated with more pronounced immunosuppression when an additional rescue therapy is added. Nonetheless, infliximab levels at initiation of cyclosporine were not associated with AEs in a study that included 40 patients, with infliximab levels available for 26 of them.[207]

In conclusion, in highly selected patients with ASUC, third-line rescue therapy may be beneficial and lead to colectomy avoidance; nonetheless, the potential benefits need to be weighed against the risk of such a strategy, including potential mortality. Both risks and benefits should be carefully discussed with the patient and the multidisciplinary team.

7. Fecal microbiota transplantation for ulcerative colitis

Practice point 3

Different therapeutic approaches have been studied as adjunctive or alternative treatments in ulcerative colitis, with varying efficacy as well as levels of evidence. Fecal microbiota transplantation has been evaluated in greater detail, even if no formal recommendations can be made [Agreement: 86%]

Fecal microbiota transplantation [FMT] is a promising approach for the treatment of UC. FMT may exert its effects by increasing microbial diversity and shifting the microbiome of the recipient patients to more closely resemble that of the healthy donor.[208] Trials have shown that FMT-treated patients with UC achieve higher clinical and endoscopic remission rates than controls in short-term studies. AEs are generally similar between FMT and controls,[209] and most AEs include transient gastrointestinal symptoms.[208] A Cochrane systematic review and meta-analysis of 10 RCTs showed similar findings favoring FMT and graded the certainty of evidence as low.[210] The authors also identified that the range of follow-up of these studies was only 6–12 weeks. The certainty of evidence was very low for FMT as maintenance therapy and did not achieve statistical significance for symptomatic or endoscopic remission endpoints.[210]

Heterogeneity exists within the mode and frequency of FMT administration; these include once-weekly enemas for 6 weeks,[211] nasoduodenal infusion,[212] colonoscopic infusion followed by five enemas weekly for 8 weeks,[213] or two enemas over 1 week.[214] Most trials used aerobic FMT processing, while one used anaerobic FMT processing, and heterogeneity existed regarding whether pre-FMT bowel lavage was used and whether FMT was fresh or frozen. Most well-powered trials did not prepare patients with antibiotics prior to FMT. Meta-analyses suggest that while administration through the lower gastrointestinal tract is more effective than placebo, upper gastrointestinal tract administration is not.[208,215] However, a more recent small RCT has suggested that oral FMT may be effective.[216] An increased number of infusions and the use of multiple stool donors also seem to increase the efficacy of FMT.[208,217] However, antibiotics, bowel preparation administered before FMT, or concomitant biologic or rectal therapy did not affect patient outcomes.[218]

Guidance for use: While multiple RCTs show encouraging data, there remains uncertainty regarding the efficacy of FMT to achieve endoscopic remission and to maintain remission after the induction period. While safety is generally reassuring, stool procurement is variable and may carry potential for contamination and subsequent impact on patients.[219] Until clarity is provided on the ideal preparation and administration frequency and on the feasibility of performing this at scale, this approach remains experimental as a therapy for UC.

8. Additional aspects of the medical management of ulcerative colitis

8.1. Multidisciplinary team approach

Practice point 4

A multidisciplinary team approach is an important element of inflammatory bowel disease care, helping to coordinate and personalize the management of complex cases. Regular multidisciplinary team meetings assist shared decision-making, reduce variation in practice, and contribute to improved outcomes and service governance [Agreement: 98%]

A multidisciplinary team approach is a cornerstone of high-quality IBD care, enabling the delivery of patient-centered, coordinated, personalized, and consensus-driven management plans, particularly for patients with more complex disease.[220] The multidisciplinary team typically comprises gastroenterologists, colorectal surgeons, IBD nurse specialists, dietitians, pharmacists, psychologists, radiologists, and pathologists, who each contribute their expertise to guide complex clinical decisions. Pediatric gastroenterologists, obstetricians, rheumatologists, dermatologists, hepatologists, oral medicine specialists, ophthalmologists, general practitioners, and social workers may also participate depending on need.[221]

Regular multidisciplinary team meetings enable collaborative decision-making for complex IBD cases, such as those requiring biologic escalation, surgery, or management of extraintestinal complications. This approach ensures guideline-aligned care, reduces variability, and improves outcomes. Governance is supported through structured meetings, documentation in electronic records, and defined roles, enhancing accountability and medico-legal protection. Patient preferences are incorporated to promote shared decision-making and consistent messaging. The multidisciplinary team model also supports professional education and has been effectively adapted for virtual and subspecialty settings, ensuring quality, continuity, and coordinated care across the IBD service.[119,222–224]

8.2. Treat-to-target approach

Practice point 5

We suggest a "treat-to-target" approach for the treatment of patients with ulcerative colitis, although consensus on the precise targets and thresholds continues to develop [Agreement: 93%]

"Treat-to-target" describes an approach in which a treatment goal is set and agreed upon following discussions between individual patients and treating clinicians, and which is to be achieved within a defined period. Progress towards that goal may be monitored using different specific targets.[14] Following initiation of any therapy, these targets are then assessed, with treatment modification considered if a target is missed.[225] This approach aims to reduce long-term complications through targeted treatment monitoring and adjustment.

However, it should be noted that most of the evidence for this approach comes from studies in CD. Therefore, debate remains regarding the optimal treatment target in UC, which may include clinical, ultrasound, endoscopic, histologic, or biochemical endpoints or even normalized QoL.[226–230] Retrospective studies have convincingly shown that mucosal healing is associated with improved long-term outcomes in patients with UC (eg, achievement of long-term [steroid-free] clinical remission and mucosal healing as well as avoidance of colectomy).[231] Moreover, long-term analyses have demonstrated that the risk of clinical relapse and the need for surgery and hospitalization are significantly lower in patients with histologic remission.[232,233] Consistent with this, a recent post-hoc analysis of two RCTs found that a fecal calprotectin concentration ≤250 µg/g was associated with an increased probability of achieving long-term clinical, endoscopic, and histologic remission and a reduced probability of colectomy and UC-related hospitalization.[234] However, in a recent prospective multicenter RCT, treatment optimization using fecal calprotectin monitoring over 12 months in addition to clinical symptoms did not improve the primary endpoint of a Mayo endoscopic subscore of 0 at 12 months [27.6% in the interventional arm vs 26.3% in the conventional arm; $P = .811$].[235] In addition, intestinal ultrasound examination may serve as a non-invasive monitoring tool.[236] Beyond this, there is a lack of interventional RCTs that explicitly compare the treat-to-target approach [beyond steroid-free clinical remission] with conventional management with respect to the long-term course of the disease and the occurrence of complications.

Furthermore, it is very important that the specific characteristics and preferences of each patient are considered when setting individual treatment goals, which should be defined as part of a shared decision-making process. Finally, treatment goals should be considered dynamic, and changes to these goals may be appropriate over time.

In summary, it appears that the relative weight given to different therapeutic targets in the development and optimization of UC treatments could be improved, with increased emphasis on endoscopic and histologic targets over clinical or symptomatic targets. However, for this evolution to occur, new research must demonstrate that the treat-to-target approach delivers better long-term outcomes compared with current approaches.[237] Until then, treat-to-target beyond steroid-free clinical remission remains a promising but not yet conclusively validated framework.

8.3. Treatment escalation

Practice point 6

Prompt treatment for ulcerative colitis is important for disease control. However, the exact timing and approach to treatment escalation for patients with ulcerative colitis requires individualized assessment and judgement [Agreement: 98%]

The most common indication for dose escalation of the same therapy is loss of response, and the most common indication for switching therapies is either loss of response or AEs.[238,239] In assessing loss of response, important factors to consider include the severity of patient symptoms, endoscopic severity, objective biomarkers [such as fecal calprotectin levels], and confirmation of negative stool cultures and *Clostridioides difficile* testing. Objective inflammation visualized with intestinal ultrasound is an emerging endpoint on which escalation decisions may also reasonably be based.[240] In patients on either conventional or advanced therapies, the presence of both active symptoms [such as increased liquid stool frequency, rectal bleeding, and often bowel urgency] and either biomarker or endoscopic evidence of inflammation should prompt action. Therapy should also be escalated in asymptomatic patients with biomarker or endoscopic evidence of inflammation that is deemed clinically meaningful by the treating healthcare professional.

In patients with active disease despite low-dose 5-ASA therapy, 5-ASA dose escalation is an effective strategy for non-severe disease.[241] For anti-TNFs, 10%–13% of patients lose response annually, and dose escalation benefits 50%–75% of these patients.[242,243] In addition, anti-TNF dose escalation in induction non-responders is associated with reduced hospitalization.[244] For ustekinumab-treated patients with UC, no studies have provided data on loss of response, but a single study showed that dose escalation occurred at 18% per person-year, with 58% of patients achieving symptomatic remission.[245] Data for IL-23 antagonist dose escalation are minimal and require further evidence before broader implementation.[148,152,154] In patients with UC on vedolizumab maintenance therapy, 40% lose response, and approximately half will recapture response with dose escalation.[246,247] Dose escalation is also efficacious for tofacitinib in

patients with non-response or loss of response to low-dose tofacitinib.[248] Less evidence is available for dose escalation with other JAKi. Preliminary data suggest possible efficacy of reinduction with 45 mg upadacitinib to recapture response.[249]

Treatment escalation can also be pursued in asymptomatic patients. In patients with UC in symptomatic remission with a Mayo endoscopic score of 1, 5-ASA dose escalation has been shown to reduce relapse rates.[250,251] In addition, in patients in symptomatic remission with elevated fecal calprotectin, 5-ASA dose escalation was associated with lower relapse rates[252] and greater reduction in fecal calprotectin.[229] Lastly, the presence of a cecal patch has not been shown to be a risk factor for proximal extension, relapse, or need for dose escalation or medication switch[253] and should not affect the decision to escalate therapy.[254]

8.4. Therapeutic drug monitoring

Practice point 7

There are insufficient data to support proactive therapeutic drug monitoring with anti-tumor necrosis factor agents, vedolizumab, or ustekinumab in the management of ulcerative colitis. We suggest reactive therapeutic drug monitoring in patients with loss of response to an anti-tumor necrosis factor agent to guide the treatment strategy [Agreement: 92%]

Therapeutic drug monitoring [TDM] is employed to optimize management in IBD.[255] Evidence supports an exposure–response relationship, with higher drug levels correlating with improved clinical outcomes. A pooled analysis of 728 patients from the ACT-1 and ACT-2 trials demonstrated an exposure–response relationship between infliximab concentrations and clinical outcomes in moderate-to-severe UC.[256] A multicenter prospective study of 182 IBD patients on maintenance anti-TNF therapy showed that patients achieving mucosal healing had significantly higher trough concentrations than those who did not [cut-offs of 3.4 µg/mL for infliximab and 7.2 µg/mL for adalimumab].[257] However, the use of proactive TDM, defined by routine measurement of trough drug levels and antibody titers during clinical remission to maintain concentrations within a therapeutic window, remains limited in IBD, including UC.

In a prospective Belgian study, 187 patients [54 with UC] managed with either ultra-proactive TDM using point-of-care testing [8.8 trough measurements per person per year] or standard reactive TDM had similar infliximab failure rates [19% vs 10%; $P = .08$] and sustained clinical remission [75% vs 83%; $P = .17$] at 12 months.[258] However, no specific data can be extracted for patients with UC in particular.

The NOR-DRUM trial was the largest prospective study of infliximab TDM, including 411 patients at induction [TDM, $n = 198$; standard, $n = 200$], of whom approximately 20% had UC.[259,260] At week 30, remission rates were similar between groups [50.5% vs 53.0%; $P = .78$], showing no benefit of proactive TDM during induction. In the maintenance phase [NOR-DRUM B, 458 patients], sustained disease control was significantly higher with TDM [73.6% vs 55.9%; $P < .001$]. Clinically significant anti-drug antibodies occurred in 9.2% [TDM] versus 15.0% [control], with similar AEs [60% vs 63%]. Subgroup analyses suggested that the maintenance benefit extended to UC. A major limitation of the study was insufficient power to assess disease-specific subgroup outcomes, leaving estimates for UC uncertain.

No meta-analysis has specifically addressed the role of TDM in patients with UC only. Several meta-analyses have investigated TDM in both CD and UC. A 2022 meta-analysis of nine RCTs involving 1405 patients with IBD treated with anti-TNF agents found no significant benefit of proactive TDM over conventional management in maintaining clinical remission.[261] Additionally, proactive TDM did not reduce the risk of developing anti-drug antibodies or SAEs. However, patients in the proactive TDM group were more likely to undergo dose escalation [RR: 1.56; 95% CI: 1.25–1.94].

A 2023 meta-analysis that included 26 studies [including nine RCTs] revealed that, compared with standard of care, proactive TDM was associated with a significantly decreased risk of treatment failure [RR: 0.64; 95% CI: 0.48–0.85] and a non-significant decrease in the need for surgery [RR: 0.51; 95% CI: 0.25–1.02] and hospitalization [RR: 0.64; 95% CI: 0.40–1.00] in patients with IBD.[262] Furthermore, compared with standard of care, proactive TDM was associated with higher rates of endoscopic remission [RR: 1.19; 95% CI: 0.93–1.53] and clinical remission [RR: 1.07; 95% CI: 0.97–1.18].[262]

A 2024 meta-analysis including nine studies [one systematic review, six RCTs, and two cohort studies] demonstrated that proactive TDM did not significantly improve 12-month clinical remission [RR: 1.16; 95% CI: 0.98–1.37] in patients with IBD.[263] However, proactive TDM was associated with lower treatment discontinuation [OR: 0.12; 95% CI: 0.05–0.27], reduced risk of acute infusion reactions [OR: 0.21; 95% CI: 0.05–0.82], fewer AEs [OR: 0.38; 95% CI: 0.15–0.98], and a lower probability of surgery, while being more cost-effective.[263]

In the situation of loss of response in active UC, reactive TDM may be used to guide the next treatment choice. In a prospective study of 59 patients with loss of response despite optimization of the first anti-TNF, switching to a second anti-TNF was less effective in those with antibodies to the first agent.[264] The same group also demonstrated that in patients with IBD receiving adalimumab with optimal trough levels [>4.9 µg/mL], switching to another class was more effective than optimizing adalimumab.[265] These findings suggest that the pharmacokinetic profile of the first anti-TNF can influence clinical outcomes with a second anti-TNF.

Limited data are available on the role of TDM with vedolizumab and ustekinumab. A meta-analysis of five cohort studies [558 patients with IBD, 42% with UC] revealed significantly higher trough levels of vedolizumab in patients achieving clinical remission [median 14.3 vs 10.5 µg/mL] and endoscopic remission [13.0 vs 9.7 µg/mL], with mean differences of 5.1 µg/mL.[266] For ustekinumab, pharmacokinetic and post-hoc analyses from phase 3 trials in UC identified an induction threshold of 3.7 µg/mL at week 8 and a steady-state maintenance trough of ≥1.3 µg/mL, both associated with significantly higher rates of clinical and endoscopic remission without added safety concerns.[267] However, clinical utility requires validation in controlled trials, particularly to guide proactive versus reactive monitoring and to determine optimal thresholds.

8.5. Sequencing advanced therapies

Practice point 8

Apart from suggesting the use of vedolizumab rather than adalimumab, no individual treatment or class of treatment can be recommended over another as first-line or subsequent therapy in the treatment of patients with moderate-to-severe ulcerative colitis. It is therefore critical that every treatment choice is individualized to the treated patient [Agreement: 98%]

Sequencing therapies in individual patients with moderate-to-severe UC is based on many factors, which among others include patient preference, disease severity, previous treatments, age, efficacy and safety profile of the chosen drug, existing comorbidities, extra-intestinal manifestations, wish to become pregnant, adherence, local availability, and prevailing federal regulations.[268] There is only one head-to-head RCT in moderate-to-severe UC, in which vedolizumab was superior to adalimumab with respect to achievement of clinical and endoscopic remission but not steroid-free clinical remission. The effect was more pronounced in biologic-naive patients than in anti-TNF-exposed patients.[142] We recommend not comparing treatment effectiveness across trials, particularly as they differ in treatment design, endpoints, and baseline characteristics of included patients. In this context, the utility of network meta-analyses to guide treatment decisions is not regarded as sufficient, as outcomes differ between analyses and do not enable adequate comparison between the investigated substances. Results of observational studies also do not offer sufficient evidence for therapy-sequencing recommendations. It is therefore critical that every treatment choice is individualized to the treated patient.

8.6. Combination of advanced therapies

Practice point 9

There is currently insufficient evidence to recommend the use of combined advanced therapies for the induction and maintenance of remission for moderate-to-severe ulcerative colitis [Agreement: 100%]

Combination of advanced therapies [biologics or small molecules] in UC is an emerging strategy aimed at enhancing treatment efficacy in patients with refractory disease. To date, only one RCT has evaluated this approach in UC. The VEGA study was a phase 2a proof-of-concept trial designed to assess whether combination therapy with guselkumab and golimumab was more effective than each agent in monotherapy for inducing clinical response in patients with moderately-to-severely active UC.[269] The primary endpoint was not met; while combination therapy was superior to golimumab alone [clinical response at week 12: 83% vs 61%; $P = .0032$], it was not significantly better than guselkumab alone [83% vs 75%; $P = .2$].[269]

However, the VEGA study presents several limitations that must be acknowledged.[269] First, the sample size was relatively small, which limited the ability to fully characterize the safety profile of the combination strategy. The study was also not designed to detect differences in clinical remission, which is the standard regulatory endpoint. Moreover, the statistical design was exploratory, using a liberal alpha threshold [two-sided $\alpha = .20$] without correction for multiple testing, which increases the potential for false-positive results. Importantly, the duration of assessment was short, as golimumab was discontinued after 10 weeks, preventing evaluation of the sustained effects or risks of longer-term combination therapy. The trial's objective was to provide preliminary data on the benefit–risk balance of short-term induction therapy. Larger and longer studies investigating both induction and maintenance regimens are currently ongoing.

Beyond VEGA, several systematic reviews and meta-analyses have explored dual therapy in IBD.[270–272] These suggest potential benefit in highly refractory patients, but the evidence is constrained by the observational nature of most studies, heterogeneous combinations, and limited long-term safety data.

In summary, while combination therapy remains a promising strategy for selected patients, current evidence is insufficient to support its routine use in clinical practice. Larger, controlled trials are needed to define its role, safety, and appropriate patient selection.

8.7. Withdrawal strategies

Practice point 10

Steroid use should be minimized. If used at high doses [≥20 mg prednisone equivalent] for more than 2 weeks, systemic corticosteroids should be tapered to minimize the risk of hypothalamic–pituitary–adrenal axis suppression. There is currently insufficient evidence to support or refute the need for tapering colonic-release corticosteroids [Agreement: 93%]

The risk of adrenal suppression increases with both the dose and duration of systemic glucocorticoid therapy.[273] Patients receiving high-dose treatment [≥20 mg/day of prednisone equivalent] for more than 2–3 weeks are at considerable risk of hypothalamic–pituitary–adrenal axis suppression. A systematic review of 73 studies assessing hypothalamic–pituitary–adrenal function after systemic glucocorticoid exposure reported a median incidence of adrenal insufficiency of 37% [range: 13%–63%].[274] In contrast, short courses of systemic glucocorticoids <2 weeks are unlikely to result in hypothalamic–pituitary–adrenal suppression.[275,276]

Oral budesonide MMX has shown efficacy for inducing remission in UC.[76] However, its utility in maintenance therapy remains uncertain, and there is no clear evidence supporting a tapering approach.

For patients with ulcerative proctitis, maintenance therapy with topical 5-ASA reduces the risk of relapse.[86–89] No tapering strategy has been formally assessed in this setting. Thus, if

Table 1. Induction and maintenance doses for approved biologics and small molecules in ulcerative colitis.

Drug	Approved induction dose	Approved maintenance dose
Infliximab	5 mg/kg IV at weeks 0, 2, and 6	5 mg/kg IV every 8 weeks 120 mg SC every 2 weeks
Adalimumab	160 mg SC at week 0 [day 1], then 80 mg SC at week 2	40 mg SC every other week
Golimumab	200 mg SC at week 0, then 100 mg SC at week 2	50 mg SC every 4 weeks [≤80 kg] or 100 mg SC every 4 weeks [≥80 kg]
Vedolizumab	300 mg IV at weeks 0, 2, and 6	300 mg IV every 8 weeks or 108 mg SC every 2 weeks
Ustekinumab	Single weight-based IV dose [~6 mg/kg] at week 0	90 mg SC every 8–12 weeks
Risankizumab	1200 mg IV at weeks 0, 4, and 8	180 mg or 360 mg SC every 8 weeks
Mirikizumab	300 mg IV at weeks 0, 4, and 8	200 mg SC every 4 weeks
Guselkumab	200 mg IV at weeks 0, 4, and 8 400 mg SC at weeks 0, 4, and 8	Either 100 mg SC every 8 weeks or 200 mg SC every 4 weeks
Tofacitinib	10 mg orally twice-daily for 8 weeks [up to 16 weeks if needed]	5 mg orally twice-daily
Upadacitinib	45 mg orally once-daily for 8 weeks [up to 16 weeks if needed]	15–30 mg orally once-daily
Filgotinib	200 mg orally once-daily for 10 weeks [up to 22 weeks if needed]	200 mg orally once-daily
Ozanimod	Titration: 0.23 mg once-daily on days 1–4, then 0.46 mg once-daily on days 5–7	0.92 mg orally once-daily
Etrasimod	2 mg orally once-daily	2 mg orally once-daily

Note: Doses reflect current label-recommended regimens. Consider individual patient factors, regional labeling, and safety warnings.
Abbreviations: IV, intravenous; SC, subcutaneous.

discontinuation is necessary, there is no evidence favoring either abrupt cessation or gradual tapering.

Practice point 11

Effective and well-tolerated therapies should be continued. Given the substantial relapse rates after withdrawal of advanced therapies, individual risk–benefit balance, evidence of deep remission, signs of residual disease activity, and risk factors of disease relapse should be carefully assessed before treatment de-escalation. If advanced therapy is withdrawn, close monitoring of biomarkers of inflammation for disease relapse should be performed [Agreement: 95%]

In the prospective, open-label HAYABUSA RCT by Kobayashi et al., 46 patients with UC were randomized either to maintain or discontinue anti-TNF treatment. At week 48, 54.3% of patients in the withdrawal arm were in remission compared with 80.4% in the anti-TNF maintenance group [$P < .05$]. Of note, concomitant therapy with 5-ASA and thiopurines was allowed after randomization.[277]

A recently published prospective, randomized, placebo-controlled trial by Gisbert et al. [the EXIT trial] reported no significantly increased rates of clinical relapse after 1 year in 140 anti-TNF-treated patients with IBD, of whom 78 had UC, although fecal calprotectin levels were significantly higher and endoscopic activity numerically higher in the withdrawal group at the end of the study compared with patients who continued anti-TNF treatment.[278] In the follow-up extension of this trial, withdrawing anti-TNF therapy was likewise not associated with a higher long-term relapse risk.[279]

A meta-analysis published in 2023 analysed 18 individual studies in patients with UC and found a clinical relapse rate of 37% after 1 year of anti-TNF withdrawal, with further increases over longer follow-up periods.[280] Identified predictive markers for relapse included lack of deep remission and prior need for dose intensification.[281–284]

Evidence for de-escalation of advanced therapies other than anti-TNF agents is scarce.[285] A prospective RCT in 62 patients with UC receiving IV vedolizumab plus thiopurine combination therapy did not find an increased relapse rate when thiopurines were discontinued.[286]

The prospective, randomized SPARE trial showed that in patients with CD in steroid-free remission receiving anti-TNF and thiopurine combination therapy, de-escalation to thiopurine monotherapy resulted in a significantly higher risk of clinical relapse compared with azathioprine withdrawal [36% vs 10%].[287] In addition, a recent meta-analysis of five RCTs in patients with IBD [mainly CD] in sustained corticosteroid-free clinical remission for more than 6 months on combination therapy found that de-escalation by withdrawing anti-TNF, but not by withdrawing immunomodulators, was associated with an increased risk of relapse.[288]

Taken together, given the chronic nature of the disease and the absence of reliable predictive markers for relapse after withdrawal, effective and well-tolerated advanced therapies should not be routinely withdrawn, but withdrawal may be considered in highly selected patients or upon patient request. If advanced therapy is withdrawn, close monitoring for signs of disease relapse is recommended.[289]

9. Conclusion

These recommendations summarize the current evidence on the medical management of adult patients with UC. Table 1 summarizes the induction and maintenance doses for approved biologics and small molecules in 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-JCC* provides alternative tools, such as Topical Reviews or Position Papers. 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 recognize 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-JCC* will disseminate these guidelines through educational activities [ie, educational platforms, ECCO Workshops, e-learning, and e-Guide] and will support any initiative to integrate ECCO guidelines into clinical practice. The *ECCO-JCC* e-Guide will serve primarily as a resource to examine how the guideline recommendations can be implemented into daily clinical practice and patient care pathways.[290]

These treatment guidelines will be regularly updated according to the Guideline Committee schedule for the update of guidelines on the *ECCO-JCC* website.

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Supplementary material

Supplementary material is available at *ECCO-JCC* online

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Conflicts of interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The conflict of interest 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 [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of the authors.

Data availability

Summary of findings tables [SOFs] produced for GRADE meta-analyses are available as Supplementary material at *ECCO-JCC* online.

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