



ECCO Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

**Tim Raine,^{a,○} Stefanos Bonovas,^{b,○} Johan Burisch,^{c,○} Torsten Kucharzik,^d
Michel Adamina,^{e,○} Vito Annese,^f Oliver Bachmann,^{g,○}
Dominik Bettenworth,^h Maria Chaparro,^{i,○}
Wladyslawa Czuber-Dochan,^j Piotr Eder,^{k,○} Pierre Ellul,^l
Catarina Fidalgo,^{m,○} Gionata Fiorino,^{n,○} Paolo Gionchetti,^o
Javier P. Gisbert,ⁱ Hannah Gordon,^p Charlotte Hedin,^{q,○} Stefan Holubar,^{r,○}
Marietta Iacucci,^s Konstantinos Karmiris,^t Konstantinos Katsanos,^u
Uri Kopylov,^v Peter L Lakatos,^{w,○} Theodore Lytras,^{x,○} Ivan Lyutakov,^y
Nurulamin Noor,^{a,○} Gianluca Pellino,^{z,aa,○} Daniele Piovani,^b
Edoardo Savarino,^{bb,○} Francesco Selvaggi,^z Bram Verstockt,^{cc,○}
Antonino Spinelli,^b Yves Panis,^{dd,○} Glen Doherty^{ee}**

^aDepartment of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK ^bDepartment of Biomedical Sciences, Humanitas University; IRCCS Humanitas Research Hospital, Milan, Italy ^cGastrounit, Medical Division, Hvidovre Hospital; Copenhagen Center for Inflammatory Bowel Disease in Children, Adolescents and Adults, Hvidovre Hospital, University of Copenhagen, Denmark ^dDepartment of Gastroenterology, Lüneburg Hospital, University of Hamburg, Lüneburg, Germany ^eDepartment of Surgery, Clinic of Visceral and Thoracic Surgery, Cantonal Hospital Winterthur, Zurich, Switzerland ^fDepartment of Biomedical Engineering, Clinical Research and Artificial Intelligence in Surgery, Faculty of Medicine, University of Basel, Allschwil, Switzerland ^gDepartment of Gastroenterology, Fakeeh University Hospital, Dubai, UAE ^hDepartment of Internal Medicine I, Siloah St. Trudpert Hospital, Pforzheim; Hannover Medical School, Hannover, Germany ⁱUniversity Hospital Munster, Department of Medicine B - Gastroenterology and Hepatology, Munster, Germany ^jGastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain ^kKing's College London, Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, London, UK ^lDepartment of Gastroenterology, Dietetics and Internal Medicine - Poznań University of Medical Sciences; Heliodor Świecicki University Hospital, Poznań, Poland ^mDepartment of Medicine, Division of Gastroenterology, Mater Dei Hospital, Msida, Malta ⁿGastroenterology Division, Hospital Beatriz Ângelo, Loures, Portugal ^oDepartment of Biomedical Sciences, Humanitas University; IBD Center, Humanitas Clinical and Research Center, Milan, Italy ^pIBD Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna DIMEC, University of Bologna, Bologna, Italy ^qDepartment of Gastroenterology, Barts Health NHS Trust, Royal London Hospital, London, UK ^rKarolinska Institutet, Department of Medicine Solna; Karolinska University Hospital, Department of Gastroenterology, Dermatovenereology and Rheumatology, Stockholm, Sweden ^sDepartment of Colon & Rectal Surgery, Cleveland Clinic, Cleveland, OH, USA ^tInstitute of Immunology and Immunotherapy, NIHR Biomedical Research Centre, University of Birmingham; Division of Gastroenterology, University Hospitals Birmingham NHS Trust, Birmingham, UK ^uDepartment of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece ^vDepartment of Gastroenterology and Hepatology, Division of Internal Medicine, University and Medical School of Ioannina, Ioannina, Greece ^wDepartment of Gastroenterology, Tel-HaShomer Sheba Medical Center, Ramat Gan, and Sackler Medical School, Tel Aviv, Israel ^xDivision of Gastroenterology, McGill University Health Centre, Montreal, QC, Canada; 1st Department of Medicine, Semmelweis University, Budapest, Hungary ^ySchool of Medicine, European University Cyprus, Nicosia,

Cyprus ^γDepartment of Gastroenterology, University Hospital 'Tsaritsa Yoanna - ISUL', Medical University Sofia, Sofia, Bulgaria ^δDepartment of Advanced Medical and Surgical Sciences, Università degli Studi della Campania 'Luigi Vanvitelli', Naples, Italy ^{αα}Colorectal Surgery, Vall d'Hebron University Hospital, Barcelona, Spain ^{bb}Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy ^{cc}Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven; Department of Chronic Diseases, Metabolism and Ageing, TARGID - IBD, Leuven, Belgium ^{dd}Department of Colorectal Surgery, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, Clichy and Université of Paris, France ^{ee}Department of Gastroenterology and Centre for Colorectal Disease, St Vincent's University Hospital, Dublin, Ireland

Corresponding author: Tim Raine, MB, PhD, MRCP, Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. Email: tim.raine@addenbrookes.nhs.uk

1. Introduction

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

Patients living with UC can have a variable disease course.¹⁰ In this document, we discuss therapeutic approaches stratified by disease severity [mildly-to-moderately active and moderately-to-severely active disease]. Attempts to define disease severity are widely used in setting clinical trial inclusion criteria and can be measured according to several different definitions.¹¹ Trial populations will inevitably vary, and we reflect the continuum of disease severity by having the moderate disease category span both broad categories. It is also important to remember that these definitions capture severity at a given point in time and may not reflect the cumulative long-term burden of disease experienced by a patient.¹²

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

2. Methods

This document was compiled following the 'Grading of Recommendations Assessment, Development, and Evaluation' [GRADE] methodology.¹⁶ A panel of 33 experts was selected by the Guidelines Committee of ECCO from a competitive pool of applicants and worked with a team of methodologists and librarians. All

panellists received training in the GRADE methodology. Additionally, six patients with UC, representing the European Federation of Crohn's and Colitis Associations [EFCCA], were invited to participate in all face-to-face meetings as full voting members.

Two domains for the medical treatment of UC were identified and used as the basis for the following two working groups based upon disease severity: mildly-to-moderately active disease and moderately-to-severely active disease. We recognise that these divisions are somewhat arbitrary, partially overlapping, and inconsistently defined; therefore, we ensured close collaboration between the working groups to ensure that key topics were covered appropriately with the aim of providing guidance applicable across the continuum of UC severity encountered in clinical practice.

Working group participants first formulated a series of specific questions using the Population, Intervention, Comparator, Outcomes [PICO] system, which were deemed to be clinically important for the medical treatment of UC. These questions were debated in a series of telephone conferences before final agreement at a meeting of the full guideline group in Vienna in November 2019. Voting on the inclusion of PICO questions was conducted, and only those achieving agreement of >80% by the panel were included in the next phase of the process. At this meeting, the panellists also ranked each outcome's importance on a scale of 1 to 9 based on the GRADE definitions.¹⁶ Scores of 7-9 indicated an outcome that is critical to patients for decision making; scores of 4-6 indicated an important outcome, but not critical; and scores of 1-3 indicated an outcome of limited importance. The panellists' agreement on outcomes' importance was assessed using the Disagreement Index, as described in the RAND/UCLA appropriateness method.¹⁷

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

Most of the evidence informing the guidelines in this document came from randomised controlled trials conducted in adult patients

with UC. The methodologists directly performed the comparisons. The risk ratio [RR] was used to measure treatment effects. Study-level RRs with 95% confidence intervals [CIs] were calculated in accordance with the intention-to-treat principle. When zero events occurred in one group of a trial, we used a continuity correction that was inversely proportional to the relative size of the other group. To synthesise the evidence, we prepared forest plots and calculated the pooled effect estimates using random-effects models [DerSimonian and Laird approach].¹⁸ We used R software for statistical analysis. All *p*-values are two-tailed. For all tests [except for heterogeneity], a *p*-value <0.05 indicates statistical significance.

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

The quality of evidence was expressed using the following four categories: high, moderate, low, and very low. For each PICO question, we rated the quality of evidence separately for each patient-important outcome, and then determined the overall quality of evidence across outcomes. For a guideline panel, the quality of evidence reflects the extent to which the confidence in the effect estimate is adequate to support a particular recommendation.¹⁶

To determine the quality of the evidence for each outcome across all studies, we started with rating the evidence from RCTs as 'high' quality, and then assessed the following five factors that could lead to down-rating the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias.¹⁶ Risk of bias was assessed using the Cochrane tool. Inconsistency was assessed with the Cochrane Q test [using a 0.10 significance level] and the I² metric [with values >50% suggesting significant heterogeneity]. Indirectness was determined according to whether the studies addressed a different but related population, intervention, or outcome from the one of interest. Imprecision was based on the number of events [the quality of evidence was downgraded by one level when the total number of events was <100, and by two levels when it was <50]. Publication bias was assessed using funnel plots, and the Begg's and Egger's tests only if there were at least 10 studies included in the meta-analysis.

The overall quality of evidence was a combined rating of the quality of evidence across all outcomes considered critical for decision making; the lowest quality of evidence for any of the critical outcomes determined the overall quality of evidence. Summary-of-Findings [SoF] tables showing all studies used in preparing each recommendation, key data and study findings for each outcome of interest, and our judgements about each of the quality of evidence factors examined are available as Supplementary material, along with documentation of the assessment of evidence quality. We present our rating of quality of evidence for: each one of the outcomes; the risk with control group; the risk with intervention group; the meta-analytic effect estimate; the anticipated absolute effects; and any other relevant information regarding the data reported in the SoF table; along with our rating of the overall quality of evidence across outcomes.

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

and nine additional reviewers from a list of ECCO members involved in ECCO guideline development [see Acknowledgements section]. The final version of all statements/recommendations was discussed among panel members during a final virtual consensus meeting in April 2021 and put to a vote; final recommendations were approved if at least 80% of the panellists agreed with the statement and its associated strength grading. The list of statements, supporting text and material, and manuscript draft were critically reviewed by the ECCO Governing Board members, who also approved the final version of these guidelines.

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

3. General Approach to the Management of Ulcerative Colitis

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

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

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

The term 'conventional therapy' has been widely used in the past to differentiate well-established traditional treatments (such as 5-aminosalicylates [5-ASA], corticosteroids, and thiopurine immunomodulators) from biologic therapies and other novel targeted small molecules. This concept is becoming somewhat outdated,

as the costs of and access to biologics therapies evolve [notably with the introduction of biosimilars] and biologics are increasingly viewed as a conventional part of UC treatment. For the purposes of this guideline, we agreed to use the term ‘conventional therapy’ as it has traditionally been understood, in the absence of any widely accepted alternative nomenclature, while also accepting the limitations of this language. Where specific definitions of conventional therapy have been used in individual studies, these are outlined in the supporting SOF tables.

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

4. Medical Management of Mildly-to-moderately Active Ulcerative Colitis

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

5-aminosalicylates

Recommendation 1

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

We performed a meta-analysis of 11 eligible RCTs with a total of 2156 patients evaluated for 4–12 weeks; 5-aminosalicylates [5-ASA] had a significantly higher efficacy in achieving **clinical remission** [RR: 1.56] versus placebo [95% CI: 1.24–1.97]. Similarly, the **clinical response** in 14 studies [total 2025 patients] evaluated at 2–10 weeks was significantly better for 5-ASA [RR: 1.58; 95% CI: 1.35–1.86] with response in 59% of patients receiving 5-ASA compared with 35% of those receiving placebo. The efficacy of 5-ASA on **endoscopic response** as evaluated in four RCTs with 416 patients investigated after 4–12 weeks was better with 5-ASA [RR: 1.73; 95% CI: 1.0–3.0]; 5-ASA was generally very well tolerated. The serious adverse event [SAE] rate evaluated in 13 studies with 2141 patients for a maximal follow-up of 12 weeks was 6.1% versus 9% in the placebo arms [RR: 0.81; 95% CI: 0.47–1.38].

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

A Cochrane meta-analysis confirmed the similar efficacy of once-daily or more frequent dosing regimens across multiple

studies.²⁹ This meta-analysis did not show any apparent differences in outcomes between different formulations of 5-ASA considered. Notably, despite discussion regarding differences of colonic distribution of different mesalazine preparations, no significant differences in outcomes were observed in any mesalazine comparator studies. For this reason, patients with mildly active UC who fail to reach remission with appropriately dosed oral 5-ASA are unlikely to achieve remission upon switching to an alternative oral 5-ASA formulation.

The same Cochrane meta-analysis did not find overall evidence for superior efficacy of higher total daily doses across multiple dose-ranging trials when compared with standard licensed doses of the same formulation.²⁹ Subgroup evaluation of the ASCEND trials suggested a benefit of 4.8 g/day of a polymer-coated formulation of mesalazine [with pH-dependent release] compared with 2.4 g/day in patients with more active disease or in those with previous treatment with corticosteroids, oral 5-ASA, rectal therapies, or multiple UC medications.^{30–32} Likewise, a post-hoc analysis of ASCEND data also showed greater rates of mucosal healing in the 4.8 g/day group than in the 2.4 g/day group.³³ In contrast, subgroup analysis restricted according to disease severity did not reveal any differences in outcomes between 4.8 g/day and 2.4 g/day in trials of a pH-dependent multimatrix (MMX) 5-ASA preparation.^{29,34}

Recommendation 2

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

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

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

Recommendation 3

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

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

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

Four trials addressed whether combined 5-ASA therapy is superior to oral monotherapy in inducing **clinical remission** in active UC.^{43–46} These studies included 322 patients and treatment duration was 3–8 weeks. All trials were heterogeneous in terms of patient characteristics, criteria used to define disease activity and remission, doses, and 5-ASA regimens. There was a serious inconsistency of evidence [$I^2 = 71\%$] and a serious risk of bias, as the methods of sequence generation and allocation concealment were unclear in three of four studies. The RR of obtaining clinical remission between combined [oral and topical] 5-ASA treatment versus oral monotherapy was 1.45 [95% CI: 0.98–2.13].

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

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

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

Topical corticosteroids

Recommendation 4

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

The use of topically administered steroids has been long established for the induction of remission in patients with proctitis and distal colitis. Topically applied steroids offer the advantage over systemic

steroids of a more targeted treatment with fewer systemic side effects; however, topical treatments may be poorly accepted by some patients due to the route of administration.

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

Recommendation 5

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

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

Topical 5-ASAs were superior for the induction of **clinical remission** [RR: 1.36; 95% CI: 1.19–1.56] but were not significantly more effective than topical steroids in inducing **clinical response** [RR: 1.09; 95% CI: 0.97–1.22]. In five studies^{68–72} including 376 patients followed for 2–4 weeks, **endoscopic response** was equally likely to be achieved with either topical 5-ASA or topical steroids [RR: 1.08; 95% CI: 0.82–1.44]. In nine studies^{61,63,65–69,71,72} including 1306 patients, the rates of SAEs did not differ between topical 5-ASA or topical steroids [RR: 1.21; 95% CI: 0.47–3.08]. Overall, the quality of evidence was rated as very low.

Although patients should generally be treated with a single topical agent, there is some [very limited] evidence to suggest that combination rectal 5-ASA and rectal corticosteroid may be of benefit. This may be appropriate for some patients who fail to respond to initial rectal therapy.⁶⁹ It is also important to be aware of differences between preparations in terms of delivery systems and formulations, all of which may have differences in patient acceptability. It is appropriate to offer a patient a trial of an alternative preparation if they are unable to tolerate an initial choice.

Colonic-release corticosteroids

Recommendation 6

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

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

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

Unlike other therapies, including 5-ASA, no data exist for the role of budesonide MMX as a maintenance therapy. This suggests that the most appropriate use of budesonide MMX may be in patients with mildly-to-moderately active disease who are not responding to or are intolerant to optimised 5-ASA therapy. An RCT comparing budesonide MMX 9 mg/day with placebo, in patients with mildly-to-moderately active UC despite oral 5-ASA therapy, revealed a significant improvement in the primary endpoint of combined clinical and endoscopic remission [13% vs 7.5%; $p = 0.049$] and histological healing in the treatment arm [27% vs 17.5%; $p = 0.016$].⁷⁷

Immunomodulators

Recommendation 7

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

Two studies have reported on the use of azathioprine as monotherapy compared with placebo for induction of remission in patients with UC.^{78,79} Overall, only 130 patients in two RCTs were analysed and assessed for **clinical remission** after 1–4 months, with azathioprine given alongside a concomitant course of corticosteroids. We performed a meta-analysis of these studies and did not

observe a difference between azathioprine and placebo for induction of clinical remission [RR: 1.22; 95% CI: 0.79–1.88] [SoF Table 7, available as [Supplementary data at ECCO-JCC online](#)]. No placebo-controlled data on clinical response, endoscopic response, or SAEs were available.

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

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

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

5-ASAs

Recommendation 8

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

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

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

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

Recommendation 9

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

We identified four placebo-controlled trials that assessed topical 5-ASA as maintenance therapy in adult patients with distal UC or proctitis [SoF Table 9, available as [Supplementary data at](#)

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

These studies did not report data on SAEs. A previous Cochrane Review found no significant difference in the proportion of patients experiencing AEs or in the rate of withdrawals due to AEs with topical 5-ASA compared with placebo.⁸⁶ Although the level of evidence is very low, our recommendation is strong, based on the long clinical experience of efficacy and minimal side effects of rectal formulations of 5-ASA along with the low cost of this intervention. It is important to consider patient acceptability; for some patients, the use of the rectal route for maintenance therapy provides significant advantages both in reducing systemic exposure to drugs and avoiding a greater level of immunosuppression. However, the rectal route of administration may present challenges for medication adherence,⁸⁸ with patients facing practical difficulties in administration and enema retention. Patient support and education may increase adherence; otherwise, alternative formulations or drugs should be considered.

Immunomodulators

Recommendation 10

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

We identified four placebo-controlled RCTs on maintenance treatment with azathioprine in patients with UC who were steroid-dependent or intolerant to 5-ASA [SoF [Table 10](#), available as [Supplementary data at ECCO-JCC online](#)].^{78,79,89,90} In 232 patients followed for 1 year, azathioprine was superior [56%] to placebo [35%] for the maintenance of clinical remission [RR: 1.59; 95% CI: 1.19–2.11]. No placebo-controlled data on endoscopic or histological remission, sustained clinical remission, or SAEs were available. In contrast to current clinical trials, different disease activity indices and endpoint definitions were used. Hence, indirect comparisons with novel and potentially more potent agents are difficult. Nevertheless, large-scale cohort studies highlighted the apparent clinical benefit of thiopurine monotherapy.⁹¹ Since we do not recommend the use of thiopurines for induction of remission, it is important that any maintenance strategy with thiopurines is planned alongside an effective induction agent. We did not identify any RCTs of thiopurines other than azathioprine, but due to their closely related pharmacology, we extend our recommendation across the drug class.

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.^{8,92–94}

No evidence supports the use of methotrexate for the maintenance of remission in UC.⁹⁵ An RCT of methotrexate against placebo

failed to demonstrate any advantage in terms of steroid-free clinical remission.⁹⁶

5. Medical Management of Moderately-to-severely Active Ulcerative Colitis

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

Systemic corticosteroids

Recommendation 11

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

Despite a limited evidence base, the use of systemic corticosteroids for the induction of remission in moderately-to-severely active UC is well established in clinical practice. The limited evidence is due in part to the large effect size and limited alternative options at the time of the original RCTs.^{97,98} A previous meta-analysis⁹⁹ included five placebo-controlled RCTs, although only two of them^{97,98} used standard systemic corticosteroids. Therefore, we performed a meta-analysis of just these two studies and calculated an RR of 2.83 [95% CI: 1.79–4.46] for the induction of **clinical remission**. The quality of evidence was rated as very low, due to a serious risk of bias, indirectness, and imprecision [in part since the number of patients included in each study was low] [SoF [Table 11](#), available as [Supplementary data at ECCO-JCC online](#)].

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

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

A 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.⁹⁹ However, none of these RCTs used a colonic-release budesonide formulation. We restrict our recommendations for budesonide MMX in mild-to-moderately active disease, and prednisolone in moderately-to-severely active UC, to reflect the study populations of the RCTs identified and the likely risk-benefit profile in these different populations.

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

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

Anti-tumour necrosis factor agents

Recommendation 12

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

We identified nine suitable RCTs that compared anti-TNF agents [infliximab, adalimumab, golimumab] with placebo in patients with moderately-to-severely active UC [SoF Table 12, available as [Supplementary data at ECCO-JCC online](#)].¹⁰³⁻¹¹¹ Patient eligibility required an inadequate response to or intolerance of conventional therapies, which were defined as corticosteroids, immunomodulators, or both in most studies, although three RCTs also permitted inadequate response to or intolerance of oral 5-ASA alone.¹⁰³⁻¹⁰⁵ Our meta-analysis revealed evidence of efficacy for induction of **clinical remission** [RR: 2.23; 95% CI: 1.81–2.76] and **clinical response** [RR: 1.56; 95% CI: 1.38–1.76]. We found data supporting efficacy for mucosal healing [RR: 1.49; 95% CI: 1.32–1.68], which is closely related to but defined differently from the outcome of interest used in this guideline [endoscopic response]; evidence was therefore downgraded due to indirectness. There was no difference in terms of AEs when analysed regardless of treatment duration [RR: 0.84; 95% CI: 0.64–1.09]. Safety data for anti-TNF agents from large cohort studies were generally reassuring.^{93,94,112}

Studies that directly compared anti-TNF agents are not available. Two network meta-analyses^{113,114} that performed indirect comparisons concluded that infliximab is superior to adalimumab for the induction of **clinical remission** [OR: 2.10; 95% CI: 1.21–3.64¹¹³ and OR: 2.10; 95% CI: 1.16–3.79, respectively¹¹⁴]. The first network meta-analysis also concluded that infliximab is superior to adalimumab and golimumab for induction of **clinical response** [OR: 2.01; 95% CI: 1.36–2.98 and OR: 1.67; 95% CI: 1.08–2.59, vs adalimumab and golimumab, respectively] and for induction of mucosal healing [OR: 1.87; 95% CI: 1.26–2.79 and OR: 1.75; 95% CI: 1.13–2.73, vs adalimumab and golimumab, respectively].¹¹³

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

were not significantly different.¹¹⁶ There are extremely limited data on the use of anti-TNF agents in other biologic sequences.

A key question is whether to combine an anti-TNF agent with an immunomodulator. The combination of infliximab with azathioprine is more effective than infliximab alone.¹¹⁷ Similar RCT-level data do not exist for adalimumab in combination with thiopurine therapy in UC, although cohort studies suggest a possible benefit for this combination¹¹⁸ and pharmacokinetic benefits have been reported in patients with Crohn's disease.¹¹⁹ For patients experiencing loss of response to a first anti-TNF agent used as monotherapy and with evidence of anti-drug antibodies, there is clear RCT evidence in favour of addition of a thiopurine to prevent formation of anti-drug antibodies to the second anti-TNF agent.¹²⁰

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

Vedolizumab

Recommendation 13

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

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

We included these two studies in a meta-analysis. **Clinical remission** was achieved more often in patients receiving vedolizumab compared with placebo [RR: 2.14; 95% CI: 1.03–4.43]. Although the direction of effect for **clinical response** was the same as for clinical remission, the difference between patients treated with vedolizumab and those receiving placebo was not significant [RR: 1.51; 95% CI: 0.99–2.29]. Rates of SAEs in patients treated with vedolizumab were not significantly different from those receiving placebo [RR: 0.71; 95% CI: 0.39–1.30]. Safety data from large cohort studies also confirmed this favourable safety assessment.¹¹²

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

The overall quality of evidence was low. The quality of evidence was low for clinical remission due to serious inconsistency and imprecision. The quality of evidence was moderate for clinical response due to serious inconsistency. The inconsistency for both outcomes

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

Tofacitinib

Recommendation 14

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

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

Further safety data are available from post-marketing studies of tofacitinib [discussed under maintenance therapy below], which should be considered when deciding upon choice of induction therapy. The potential benefits of an oral route of administration and the lack of immunogenicity should also be considered. A previous meta-analysis of RCTs on tofacitinib showed similar positive data for clinical and endoscopic endpoints in both the subgroup of patients naïve to anti-TNF agents and the subgroup with previous anti-TNF agent exposure.¹²⁶ There were no significant differences in estimates of effect sizes between these subgroups. This was reflected in the findings of indirect network meta-analyses that did not find evidence of a statistical difference between tofacitinib and anti-TNF agents or ustekinumab for clinical and endoscopic outcomes in patients naïve to biologic therapy,^{113,114} but suggest a possible benefit over adalimumab or vedolizumab for patients with previous anti-TNF agent exposure.¹¹⁴

Ustekinumab

Recommendation 15

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

A single RCT compared ustekinumab with placebo for induction therapy in patients with moderately-to-severely active UC [SoF Table 15, available as [Supplementary data at ECCO-JCC online](#)].¹²⁷

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, 51.1% of randomised patients had previously failed treatment with an alternative biologic, including 16.6% who failed treatment with both an anti-TNF agent and vedolizumab. The study demonstrated the benefit of ustekinumab [6 mg/kg] over placebo in induction of **clinical remission** [15.5% vs 5.3%; RR: 2.91; 95% CI: 1.72–4.94], **clinical response** [61.8% vs 31.3%; RR: 1.97; 95% CI: 1.64–2.37], and **endoscopic improvement** [27.0% vs 13.8%; RR: 1.96; 95% CI: 1.41–2.72].

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

Clinical and endoscopic benefit compared with placebo was observed for patients with and without previous biologic failure. An indirect network meta-analysis did not reveal a statistical difference between ustekinumab and anti-TNF agents or tofacitinib for clinical and endoscopic outcomes in patients naïve to biologic therapy, but suggested a possible benefit of ustekinumab over adalimumab or vedolizumab for patients with previous anti-TNF exposure.¹¹⁴

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

Anti-TNF agents

Recommendation 16

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

We performed a meta-analysis of data extracted from 10 placebo-controlled RCTs of anti-TNF agents [infliximab, golimumab, adalimumab] for the maintenance of remission in adult patients with moderately-to-severely active UC [SoF Table 16, available as [Supplementary data at ECCO-JCC online](#)].^{103–111,128} Anti-TNF agents were effective for the maintenance of **clinical remission** [RR: 1.98; 95% CI: 1.60–2.45], **steroid-free clinical remission** [RR: 2.86; 95% CI: 1.67–4.90], **improvement in quality of life [QoL]** [RR: 1.71; 95% CI: 1.27–2.32], and **sustained clinical remission** [RR: 2.76; 95% CI: 1.78–4.28]. The risk of SAEs was not different between anti-TNF agents and placebo [RR: 0.84; 95% CI: 0.64–1.09]. Evidence was also sought for endoscopic remission and biochemical remission; however, data were insufficient. Large-scale cohort studies support the safety of these drugs.^{93,94,112}

Recommendation 17

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

Multiple studies have shown an association between trough levels of biologic agents, including anti-TNF agents,¹²⁹⁻¹³⁴ vedolizumab,¹³⁵⁻¹³⁷ and ustekinumab,¹³⁸ and clinical outcomes in UC. Nonetheless, these studies were all retrospective analyses and cannot confirm any causal effect or suggest a benefit of trough-level based dose adjustment for improvement of response to biologics in patients with persistent disease activity. Retrospective analyses of mixed cohorts of patients with IBD, experiencing loss of response to anti-TNF agents, have shown that measurement of adequate infliximab or adalimumab drug levels appears to correlate well with patients who do not respond to subsequent dose escalation and to patients who do respond to switching to non anti-TNF therapies.¹³⁹⁻¹⁴¹ These retrospective data suggest that decisions informed by drug monitoring may be more likely to be successful than clinically guided decision making alone,¹⁴⁰ but this requires validation in a prospective study.

The same challenges and arguments around the need to demonstrate benefit and not just association apply to discussions around the use of prospective monitoring of drug levels to guide dosing in patients who are not experiencing loss of response. One study, published in abstract only, randomised 371 participants with UC, who had responded to induction therapy with adalimumab, to receive adalimumab at standard dose [40 mg every other week], high dose [40 mg every week], or dosing guided by therapeutic drug monitoring.¹⁴² The therapeutic drug monitoring arm was not powered to demonstrate superiority and was considered exploratory. There was a non-significant trend towards higher rates of clinical remission amongst responders to induction therapy who were randomised to receive drug monitoring-guided dosing compared with standard dose [36.5% vs 29%].

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

Vedolizumab

Recommendation 18

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

We identified three RCTs that included 441 patients treated with intravenous vedolizumab or placebo, 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 18, available as [Supplementary data at ECCO-JCC online](#)].^{122,123,143,144} Patients in these trials were followed up for 52–60 weeks. We performed a meta-analysis of results from these trials. **Clinical remission** was more common in induction-responders who subsequently received vedolizumab compared with placebo [RR: 2.37; 95% CI: 1.74–3.23]. Likewise, **sustained clinical remission** was also more common in patients receiving vedolizumab maintenance therapy compared with placebo [20.7% vs 9.4%; RR: 2.16; 95% CI: 1.34–3.50]. The quality of evidence for these outcomes was moderate to high. The rate of SAEs across five studies involving 1288 patients was not significantly different between vedolizumab and placebo [RR: 0.71; 95% CI: 0.39–1.30]. The quality of evidence for this outcome was moderate due to serious imprecision arising from sparse data. Nevertheless, the safety profile of vedolizumab has been established in a large cohort study.¹¹² In

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

More recently, a double-dummy placebo-controlled RCT evaluated both intravenous and subcutaneous preparations of vedolizumab in patients with moderately-to-severely active UC, who had responded to open-label intravenous vedolizumab induction therapy.¹⁴³ **Clinical remission, endoscopic improvement, and sustained clinical remission** were significantly more frequently observed with subcutaneous vedolizumab than with placebo. The study was not powered to compare intravenous and subcutaneous preparations, although all outcomes were numerically similar between these two groups. SAEs occurred at similar frequencies in all three groups, and no distinct safety signals were observed with the subcutaneous preparation.

Recommendation 19

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

One RCT compared the efficacy and safety of vedolizumab with those of adalimumab over a 1-year period in patients with moderately-to-severely active UC [SoF Table 19, available as [Supplementary data at ECCO-JCC online](#)].¹¹⁶ A significantly higher percentage of patients in the vedolizumab group than in the adalimumab group achieved **clinical response** [RR: 1.46; 95% CI: 1.29–1.67], **clinical remission** [RR: 1.39; 95% CI: 1.10–1.76], and **endoscopic remission** [RR: 1.43; 95% CI: 1.17–1.75]. There was a numerical trend in favour of vedolizumab for **biochemical remission** [RR: 1.22; 95% CI: 0.96–1.54]. Corticosteroid-free clinical remission occurred in a numerically lower percentage of patients in the vedolizumab group than in the adalimumab group [RR: 0.58; 95% CI: 0.32–1.05]. Of note, the quality of evidence for steroid-free clinical remission was low, as evidence relied on sparse data and the confidence intervals were very wide. Incidence rates of infections and serious infections occurred at similar frequencies with vedolizumab and with adalimumab [RR: 0.80; 95% CI: 0.55–1.17]. It is important to note that dose escalation was not permitted with either drug, despite evidence of improved maintenance outcomes with dose escalation for both drugs.^{122,142,143}

Tofacitinib

Recommendation 20

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

We identified one RCT that reported outcomes in 593 patients treated with tofacitinib or placebo as maintenance therapy.¹²⁵ For patients who responded to induction therapy, tofacitinib at a dose of 5 or 10 mg twice daily was superior to placebo in maintaining **clinical remission** [RR: 3.37; 95% CI: 2.23–5.10] and **endoscopic remission** [RR: 3.88; 95% CI: 1.90–7.95] in patients with moderate-to-severe

UC who had an adequate response to the induction scheme. However, the evidence regarding endoscopic remission was downgraded due to imprecision [low number of events]. **Sustained clinical remission** [RR: 4.71; 95% CI: 2.51–8.84], **corticosteroid-free remission** [RR: 2.54; 95% CI: 1.39–4.65], and improvement in QoL [RR: 2.55; 95% CI: 1.93–3.37] were also superior. The evidence regarding corticosteroid-free clinical remission was also downgraded due to imprecision. Data on biochemical remission were insufficient.

SAEs for tofacitinib therapy in RCTs were comparable to placebo [RR: 0.70; 95% CI: 0.45–1.08]. The evidence was again downgraded due to imprecision. However, an increased risk for infections was observed [OR: 1.56; 95% CI: 1.18–2.06]. Most of the serious infections were of bacterial origin, including community-acquired pneumonia and urinary tract and skin infections. A separate meta-analysis of the safety profile of Janus kinase inhibitors across multiple inflammatory diseases showed a particularly high risk of viral infections, especially herpes zoster [RR: 6.53; 95% CI: 0.86–49.58].¹⁴⁶ This signal was also observed in a pooled analysis of safety data from the tofacitinib development programme in UC [incidence rate 4.1 events per 100 person-years; 95% CI: 3.1–5.2],¹⁴⁷ although most cases were uncomplicated and associated with a single dermatome. This risk appears to be dose dependent and is more common with 10 mg twice daily dosing than 5 mg twice daily.¹⁴⁷ A large cohort study in rheumatoid arthritis suggested that the rates of herpes zoster appear higher with tofacitinib than with anti-TNF agents; this risk appeared to be especially significant in older patients or in those receiving concomitant corticosteroid therapy.¹⁴⁸

A safety study of tofacitinib in patients with rheumatoid arthritis, aged ≥ 50 years and with at least one known cardiovascular risk factor, revealed a significantly increased risk of venous thromboembolism [VTE] in patients treated with 10 mg twice daily tofacitinib compared with patients treated with anti-TNF agents. This risk was not observed in patients treated with 5 mg twice daily tofacitinib.¹⁴⁹ Although data are sparse, VTE has been reported in patients with VTE risk factors who participated in the UC development programme.¹⁵⁰ Considering these findings, the European Medicines Agency recommended using tofacitinib at the lowest efficacious dose and avoiding tofacitinib 10 mg twice daily as maintenance treatment for patients with known VTE risk factors. In this regard, 140 UC patients treated with tofacitinib 10 mg twice daily for at least 2 consecutive years, and in sustained remission for ≥ 6 months, were randomised to continue with the same dose or de-escalate to 5 mg twice daily. After 6 months, clinical remission rates were 77% and 90% for the 5 mg twice daily and 10 mg twice daily groups, respectively. No differences in AEs or SAEs were detected between the two groups, although herpes zoster cases were numerically higher in the 10 mg twice daily group.¹⁵¹ Further post-marketing surveillance data suggest that tofacitinib use is also associated with an increased risk of cardiac events and malignancies.¹⁵² Overall, we reiterate the comments made previously that the efficacy data, including in patients with previous anti-TNF exposure, along with the benefits associated with oral dosing and lack of immunogenicity, support our recommendations for tofacitinib as a treatment option in patients with UC, with the risks and benefits to be considered for each patient.

Ustekinumab

Recommendation 21

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

A single RCT compared ustekinumab with placebo for maintenance therapy in UC in patients who responded to ustekinumab induction therapy.¹²⁷ The study revealed that maintenance treatment with ustekinumab, at approved dosing of 90 mg subcutaneously every 8 weeks, offers benefit when compared with placebo in maintenance of **clinical remission** [RR: 1.82; 95% CI: 1.33–2.49] and maintenance of **steroid-free clinical remission** [RR: 1.79; 95% CI: 1.30–2.47], at Week 44. Although data were not available for endoscopic improvement, we used data for the closely related endpoint of **endoscopic remission** and found benefit compared with placebo [RR: 1.79; 95% CI: 1.36–2.36]. There was a reduction in mean faecal calprotectin for those who remained on ustekinumab during the maintenance period [-434.9 vs 813.3]. The benefits of ustekinumab were also reflected by the IBDQ scores in patients who completed the maintenance study [3.9 vs -15.7]. SAEs did not occur more frequently in the treatment arm [5.2% vs 7.9%; RR: 0.67; 95% CI: 0.39–1.17].

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.¹²⁷

6. Conclusion

These recommendations summarise the current evidence on the medical management of adult patients with UC. Gaps were identified during the analysis of the data, which should be addressed by further research. Where evidence is lacking or is very weak and evidence-based recommendations cannot be given, ECCO provides alternative tools, such as Topical Reviews^{28,95,153–158} or Position Papers.^{159–161} It is important that clinicians use these guidelines within the framework of local regulations, and seek to understand and address the individual needs and expectations of every patient. We recognise that constraints on health care resources are an important factor in determining whether recommendations can be implemented for patients in many countries. The recommendations outlined here should be used to inform treatment decisions and form part of an overall multidisciplinary treatment plan for patients with UC, which may also encompass psychological, nutritional, and other non-pharmacological interventions. ECCO will disseminate these guidelines by educational activities [i.e., educational platforms, ECCO Workshops, e-learning, and e-Guide] and will support any initiative to integrate ECCO Guidelines into clinical practice; the ECCO e-Guide will primarily serve as a resource to examine how the guideline recommendations can be implemented into daily clinical practice and patient care pathways.¹⁶² The e-Guide addresses important practical issues not addressed here, such as how to monitor for both positive and negative effects of medications. These treatment guidelines will be regularly updated according to the Guideline Committee schedule for the update of guidelines on the ECCO website. Updates will use the GRADE approach and consider the most recent evidence emerging from clinical research in the field.

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Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of JCC, but are also open to public scrutiny on the ECCO website [<https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html>], providing a comprehensive overview of potential conflicts of interest of the authors.

Disclaimer

The ECCO consensus guidelines are targeted at health care professionals only and are based on an international consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO consensus guidelines. ECCO and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO consensus guidelines.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

- Maaser C, Sturm A, Vavricka SR, *et al.* ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;13:144–64K.
- Sturm A, Maaser C, Calabrese E, *et al.* ECCO-ESGAR guideline for diagnostic assessment in IBD part 2: IBD scores and general principles and technical aspects. *J Crohns Colitis* 2019;13:273–84.
- Magro F, Langner C, Driessen A, *et al.*; European Society of Pathology (ESP); European Crohn's and Colitis Organisation (ECCO). European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013;7:827–51.
- Kemp K, Dibley L, Chauhan U, *et al.* Second N-ECCO consensus statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis. *J Crohns Colitis* 2018;12:760–76.
- Harbord M, Annese V, Vavricka SR, *et al.*; European Crohn's and Colitis Organisation. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;10:239–54.
- Annese V, Beaugerie L, Egan L, *et al.*; ECCO. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;9:945–65.
- Dignass AU, Gasche C, Bettenworth D, *et al.*; European Crohn's and Colitis Organisation [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis* 2015;9:211–22.
- Kucharzik T, Ellul P, Greuter T, *et al.* ECCO guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. *J Crohns Colitis* 2021;15:879–913.
- Adamina M, Angriman I, Bemelman WA, *et al.* European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015. doi: 10.1016/j.crohns.2014.08.012.
- Burisch J, Katsanos KH, Christodoulou DK, *et al.* Natural disease course of ulcerative colitis during the first five years of follow-up in a European population-based inception cohort – an Epi-IBD Study. *J Crohns Colitis* 2019;13:198–208.
- Walsh AJ, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol* 2016;13:567–79.
- Ghosh S, Sensky T, Casellas F, *et al.* A global, prospective, observational study measuring disease burden and suffering in patients with ulcerative colitis, using the pictorial representation of illness and self-measure tool. *J Crohns Colitis* 2021;15:228–37.
- Silverberg MS, Satsangi J, Ahmad T, *et al.* Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19[Suppl A]:5A–36A.
- Lee HS, Park SH, Yang SK, *et al.* Long-term prognosis of ulcerative colitis and its temporal change between 1977 and 2013: A hospital-based cohort study from Korea. *J Crohns Colitis* 2015;9:147–55.
- Burisch J, Ungaro R, Vind I, *et al.* Proximal disease extension in patients with limited ulcerative colitis: A Danish population-based inception cohort. *J Crohns Colitis* 2017;11:1200–4.
- Schünemann H, Brożek J, Guyatt G, Oxman A. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. 2013. <https://gdt.gradepro.org/app/handbook/handbook.html>. Accessed 27 October 2021.
- Fitch K, Bernstein SJ, Aguilar MD, *et al.* *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND Corporation; 2001. https://www.rand.org/pubs/monograph_reports/MR1269.html.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986. doi: 10.1016/0197-2456(86)90046-2.
- Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis* 2012;18:1356–63.
- Sewitch MJ, Abrahamowicz M, Bitton A, *et al.* Psychological distress, social support, and disease activity in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001. doi: 10.1016/S0002-9270(01)02363-2.
- Lewis JD, Scott FI, Brensinger CM, *et al.* Increased mortality rates with prolonged corticosteroid therapy when compared with antitumor necrosis factor- α -directed therapy for inflammatory bowel disease. *Am J Gastroenterol* 2018;113:405–17.
- Murthy SK, Begum J, Benchimol EI, *et al.* Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. *Gut* 2020;69:274–82.
- Lo B, Vind I, Vester-Andersen MK, Bendtsen F, Burisch J. Direct and indirect costs of inflammatory bowel disease: ten years of follow-up in a Danish population-based inception cohort. *J Crohns Colitis* 2020;14:53–63.

24. Turner D, Ricciuto A, Lewis A, et al.; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021;160:1570–83.
25. Leung CM, Tang W, Kyaw M, et al. Endoscopic and histological mucosal healing in ulcerative colitis in the first year of diagnosis: results from a population-based inception cohort from six countries in Asia. *J Crohns Colitis* 2017;11:1440–8.
26. Laharie D, Filippi J, Roblin X, et al. Impact of mucosal healing on long-term outcomes in ulcerative colitis treated with infliximab: A multicenter experience. *Aliment Pharmacol Ther* 2013. doi: [10.1111/apt.12289](https://doi.org/10.1111/apt.12289).
27. Theede K, Kiszka-Kanowitz M, Nordgaard-Lassen I, Mertz Nielsen A. The impact of endoscopic inflammation and mucosal healing on health-related quality of life in ulcerative colitis patients. *J Crohns Colitis* 2015;9:625–32.
28. Doherty G, Katsanos KH, Burisch J, et al. European Crohn's and Colitis Organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J Crohns Colitis* 2018;12:17–31.
29. Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2020. doi: [10.1002/14651858.CD000543.pub5](https://doi.org/10.1002/14651858.CD000543.pub5).
30. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;100:2478–85.
31. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared with 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol* 2007;21:827–34.
32. Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009;137:1934–43.e1–3.
33. Lichtenstein GR, Ramsey D, Rubin DT. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing—ASCEND I and II combined analysis. *Aliment Pharmacol Ther* 2011;33:672–8.
34. Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007;132:66–75; quiz 432–3.
35. Campieri M, De Franchis R, Bianchi Porro G, Ranzi T, Brunetti G, Barbara L. Mesalazine (5-aminosalicylic acid) suppositories in the treatment of ulcerative proctitis or distal proctosigmoiditis. A randomized controlled trial. *Scand J Gastroenterol* 1990;25:663–8.
36. Campieri M, Gionchetti P, Belluzzi A, et al. Topical treatment with 5-aminosalicylic acid in distal ulcerative colitis by using a new suppository preparation. A double-blind placebo controlled trial. *Int J Colorectal Dis* 1990;5:79–81.
37. Campieri M, Gionchetti P, Belluzzi A, et al. Sucralfate, 5-aminosalicylic acid and placebo enemas in the treatment of distal ulcerative-colitis. *Eur J Gastroenterol Hepatol* 1991;3:41–4.
38. Campieri M, Gionchetti P, Belluzzi A, et al. Optimum dosage of 5-aminosalicylic acid as rectal enemas in patients with active ulcerative colitis. *Gut* 1991;32:929–31.
39. Hanauer SB. Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: Results of a multicentered placebo-controlled trial. *Inflamm Bowel Dis* 1998. doi: [10.1097/00054725-199805000-00001](https://doi.org/10.1097/00054725-199805000-00001).
40. Möller C, Kiviluoto O, Santavirta S, Holtz A. Local treatment of ulcerative proctitis with salicylazosulphapyridine (Salazopyrin) enema. *Clin Trials J* 1978;15:199–203.
41. Pokrotnieks J, Marlicz K, Paradowski L, Margus B, Zaborowski P, Greinwald R. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: A double-blind, randomized, placebo-controlled study. *Aliment Pharmacol Ther* 2000. doi: [10.1046/j.1365-2036.2000.00784.x](https://doi.org/10.1046/j.1365-2036.2000.00784.x).
42. Williams CN, Haber G, Aquino JA. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using ^{99m}Tc-labeled 5-ASA suppositories. *Dig Dis Sci* 1987;32:71–5S.
43. Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: A randomised, double blind, placebo controlled study. *Gut* 2005. doi: [10.1136/gut.2004.060103](https://doi.org/10.1136/gut.2004.060103).
44. Vecchi M, Meucci G, Gionchetti P, et al. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. *Aliment Pharmacol Ther* 2001;15:251–6.
45. Frühmorgen P, Demling L. On the efficacy of ready-made-up commercially available salicylazosulphapyridine enemas in the treatment of proctitis, proctosigmoiditis and ulcerative colitis involving rectum, sigmoid and descending colon. *Hepatogastroenterology* 1980;27:473–6.
46. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997. doi: [10.1016/0016-5085\(95\)27940-7](https://doi.org/10.1016/0016-5085(95)27940-7).
47. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997;40:775–81.
48. De Cassan C, Fiorino G, Danese S. Second-generation corticosteroids for the treatment of Crohn's disease and ulcerative colitis: more effective and less side effects? *Dig Dis* 2012;30:368–75.
49. Rubin DT, Sandborn WJ, Bosworth B, et al. Budesonide foam has a favorable safety profile for inducing remission in mild-to-moderate ulcerative proctitis or proctosigmoiditis. *Dig Dis Sci* 2015;60:3408–17.
50. Cohen RD, Dalal SR. Systematic review: rectal therapies for the treatment of distal forms of ulcerative colitis. *Inflamm Bowel Dis* 2015;21:1719–36.
51. Christophi GP, Rengarajan A, Ciorba MA. Rectal budesonide and mesalamine formulations in active ulcerative proctosigmoiditis: efficacy, tolerance, and treatment approach. *Clin Exp Gastroenterol* 2016;9:125–30.
52. Zeng J, Lv L, Mei ZC. Budesonide foam for mild to moderate distal ulcerative colitis: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2017. doi: [10.1111/jgh.13604](https://doi.org/10.1111/jgh.13604).
53. Cohen RD, Weisshof R. A comprehensive review of topical therapies for distal ulcerative colitis. *Gastroenterol Hepatol* 2020;16:21–7.
54. Watkinson G. Treatment of ulcerative colitis with topical hydrocortisone hemisuccinate sodium. *BMJ* 1958. doi: [10.1136/bmj.2.5104.1077](https://doi.org/10.1136/bmj.2.5104.1077).
55. Lennard-Jones JE, Baron JH, Connell AM, Jones FA. A double blind controlled trial of prednisolone-21-phosphate suppositories in the treatment of idiopathic proctitis. *Gut* 1962. doi: [10.1136/gut.3.3.207](https://doi.org/10.1136/gut.3.3.207).
56. Danielsson Å, Löfberg R, Persson T, et al. A steroid enema, budesonide, lacking systemic effects for the treatment of distal ulcerative colitis or proctitis. *Scand J Gastroenterol* 1992. doi: [10.3109/00365529209011158](https://doi.org/10.3109/00365529209011158).
57. Hanauer SB, Robinson M, Pruitt R, et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: A dose-ranging study. *Gastroenterology* 1998. doi: [10.1016/S0016-5085\(98\)70131-3](https://doi.org/10.1016/S0016-5085(98)70131-3).
58. Sandborn WJ, Bosworth B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. *Gastroenterology* 2015. doi: [10.1053/j.gastro.2015.01.037](https://doi.org/10.1053/j.gastro.2015.01.037).
59. Porro GB, Ardizzone S, Petrillo M, Fasoli A, Molteni P, Imbesi V. Low Pentasa dosage versus hydrocortisone in the topical treatment of active ulcerative colitis: a randomized, double-blind study. *Am J Gastroenterol* 1995. doi: [10.1111/j.1572-0241.1995.tb09309.x](https://doi.org/10.1111/j.1572-0241.1995.tb09309.x).
60. Senagore AJ, MacKeigan JM, Scheider M, Ebrom JS. Short-chain fatty acid enemas: a cost-effective alternative in the treatment of nonspecific proctosigmoiditis. *Dis Colon Rectum* 1992;35:923–7.
61. Farup PG, Hovde O, Halvorsen FA, Raknerud N, Brodin U. Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis: a comparison of the efficacy and practicality of two topical treatment regimens. *Scand J Gastroenterol* 1995. doi: [10.3109/00365529509093256](https://doi.org/10.3109/00365529509093256).

62. Danish 5-ASA Group. Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. *Dig Dis Sci* 1987;32:598–602.
63. Biancone L, Gionchetti P, Blanco Gdel V, *et al.* Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: a multicenter, randomized, double-blind study. *Dig Liver Dis* 2007;39:329–37.
64. Friedman LS, Richter JM, Kirkham SE, DeMonaco HJ, May RJ. 5-Aminosalicylic acid enemas in refractory distal ulcerative colitis: a randomized, controlled trial. *Am J Gastroenterol* 1986;81:412–8.
65. Gionchetti P, D'Arienzo A, Rizzello F, *et al.*; Italian BDP Study Group. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial. *J Clin Gastroenterol* 2005;39:291–7.
66. Hartmann F, Stein J; BudMesa-Study Group. Clinical trial: controlled, open, randomized multicenter study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2010;32:368–76.
67. Lee FI, Jewell DP, Mani V, *et al.* A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. *Gut* 1996. doi: [10.1136/gut.38.2.229](https://doi.org/10.1136/gut.38.2.229).
68. Lémann M, Galian A, Rutgeerts P, *et al.* Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1995. doi: [10.1111/j.1365-2036.1995.tb00421.x](https://doi.org/10.1111/j.1365-2036.1995.tb00421.x).
69. Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol* 1996;8:549–53.
70. Mulder CJ, Tytgat GN, Wiltink EHH, Houthoff HJ. Comparison of 5-aminosalicylic acid (3 g) and prednisolone phosphate sodium enemas (30 mg) in the treatment of distal ulcerative colitis: A prospective, randomized, double-blind trial. *Scand J Gastroenterol* 1988. doi: [10.3109/00365528809090161](https://doi.org/10.3109/00365528809090161).
71. Campieri M, Lanfranchi GA, Bazzocchi G, *et al.* Treatment of ulcerative colitis with high-dose 5-aminosalicylic acid enemas. *Lancet* 1981. doi: [10.1016/S0140-6736\(81\)90523-7](https://doi.org/10.1016/S0140-6736(81)90523-7).
72. Danish 5-ASA Group. Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. *Dig Dis Sci* 1987. doi: [10.1007/BF01296159](https://doi.org/10.1007/BF01296159).
73. Sandborn WJ, Travis S, Moro L, *et al.* Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. *Gastroenterology* 2012;143:1218–26.e2.
74. Travis SPL, Danese S, Kupcinskas L, *et al.* Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: Results from the randomised CORE II study. *Gut* 2014. doi: [10.1136/gutjnl-2012-304258](https://doi.org/10.1136/gutjnl-2012-304258).
75. Therapeutic Goods Administration. Extract from: *Clinical Evaluation Report for Budesonide*. <https://www.tga.gov.au/sites/default/files/auspar-budesonide-160111-cer.pdf>. Accessed 27 October 2021.
76. Sandborn WJ, Danese S, D'Haens G, *et al.* Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: Pooled analysis of two phase 3 studies. *Aliment Pharmacol Ther* 2015. doi: [10.1111/apt.13076](https://doi.org/10.1111/apt.13076).
77. Rubin DT, Cohen RD, Sandborn WJ, *et al.* Budesonide multimatrix is efficacious for mesalamine-refractory, mild to moderate ulcerative colitis: a randomised, placebo-controlled trial. *J Crohns Colitis* 2017;11:785–91.
78. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974;4:627–30.
79. Sood A, Midha V, Sood N, Kaushal V. Role of azathioprine in severe ulcerative colitis: One-year, placebo- controlled, randomized trial. *Indian J Gastroenterol* 2000;19:14–6.
80. Miner P, Hanauer S, Robinson M, Schwartz J, Arora S. Safety and efficacy of controlled-release mesalamine for maintenance of remission in ulcerative colitis. Pentasa UC Maintenance Study Group. *Dig Dis Sci* 1995;40:296–304.
81. Qiu X, Ma J, Wang K, Zhang H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: A systematic review with meta-analysis. *Oncotarget* 2017. doi: [10.18632/oncotarget.13715](https://doi.org/10.18632/oncotarget.13715).
82. D'Albasio G, Paoluzi P, Campieri M, *et al.* Maintenance treatment of ulcerative proctitis with mesalazine suppositories: A double-blind placebo-controlled trial. *Am J Gastroenterol* 1998. doi: [10.1016/S0002-9270\(98\)00108-7](https://doi.org/10.1016/S0002-9270(98)00108-7).
83. D'Arienzo A, Panarese A, D'Armiento FP, *et al.* 5-Aminosalicylic acid suppositories in the maintenance of remission in idiopathic proctitis or proctosigmoiditis: a double-blind placebo-controlled clinical trial. *Am J Gastroenterol* 1990;85:1079–82.
84. Hanauer S, Good LI, Goodman MW, *et al.* Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. *Am J Gastroenterol* 2000. doi: [10.1016/S0002-9270\(00\)00977-1](https://doi.org/10.1016/S0002-9270(00)00977-1).
85. Marteau P, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. *Gut* 1998;42:195–9.
86. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012;11:CD004118.
87. Biddle WL, Greenberger NJ, Swan JT, McPhee MS, Miner PB. 5-Aminosalicylic acid enemas: Effective agent in maintaining remission in left-sided ulcerative colitis. *Gastroenterology* 1988. doi: [10.1016/0016-5085\(88\)90569-0](https://doi.org/10.1016/0016-5085(88)90569-0).
88. D'Incà R, Bertomoro P, Mazzocco K, Vettorato MG, Rumiati R, Sturniolo GC. Risk factors for non-adherence to medication in inflammatory bowel disease patients. *Aliment Pharmacol Ther* 2008;27:166–72.
89. Hawthorne AB, Logan RF, Hawkey CJ, *et al.* Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992;305:20–2.
90. Sood A, Kaushal V, Midha V, Bhatia KL, Sood N, Malhotra V. The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. *J Gastroenterol* 2002;37:270–4.
91. Stournaras E, Qian W, Pappas A, *et al.*; UK IBD BioResource Investigators. Thiopurine monotherapy is effective in ulcerative colitis but significantly less so in Crohn's disease: long-term outcomes for 11 928 patients in the UK inflammatory bowel disease bioresource. *Gut* 2021;70:677–86.
92. Beaugerie L, Brousse N, Bouvier AM, *et al.* Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009. doi: [10.1016/S0140-6736\(09\)61302-7](https://doi.org/10.1016/S0140-6736(09)61302-7).
93. Kirchgerner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;155:337–46.e10.
94. Lemaitre M, Kirchgerner J, Rudnichi A, *et al.* Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA* 2017;318:1679–86.
95. Raine T, Verstockt B, Kopylov U, *et al.* ECCO topical review: Refractory IBD. *J Crohns Colitis* 2021;15:1605–20.
96. Herfarth H, Barnes EL, Valentine JF, *et al.*; Clinical Research Alliance of the Crohn's and Colitis Foundation. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. *Gastroenterology* 2018;155:1098–108.e9.
97. Truelove SC, Horler AR, Richards WC. Serial biopsy in ulcerative colitis. *Br Med J* 1955;2:1590–3.
98. Lennard-Jones JE, Longmore AJ, Newell AC, Wilson CW, Jones FA. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. *Gut* 1960. doi: [10.1136/gut.1.3.217](https://doi.org/10.1136/gut.1.3.217).
99. Ford AC, Bernstein CN, Khan KJ, *et al.* Glucocorticosteroid therapy in inflammatory bowel disease: Systematic review and meta-analysis. *Am J Gastroenterol* 2011. doi: [10.1038/ajg.2011.70](https://doi.org/10.1038/ajg.2011.70).
100. Schoon EJ, Bollani S, Mills PR, *et al.* Bone mineral density in relation to efficacy and side effects of budesonide and prednisolone in

- Crohn's disease. *Clin Gastroenterol Hepatol* 2005. doi: [10.1016/S1542-3565\(04\)00662-7](https://doi.org/10.1016/S1542-3565(04)00662-7).
101. Hall NJ, Rubin GP, Hungin AP, Dougall A. Medication beliefs among patients with inflammatory bowel disease who report low quality of life: a qualitative study. *BMC Gastroenterol* 2007;7:20.
 102. Westwood N, Travis SP. Review article: what do patients with inflammatory bowel disease want for their clinical management? *Aliment Pharmacol Ther* 2008;27[Suppl 1]:1–8.
 103. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
 104. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014. doi: [10.1053/j.gastro.2013.05.048](https://doi.org/10.1053/j.gastro.2013.05.048).
 105. Hibi T, Imai Y, Senoo A, Ohta K, Ukyo Y. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). *J Gastroenterol* 2017. doi: [10.1007/s00535-017-1326-1](https://doi.org/10.1007/s00535-017-1326-1).
 106. Kobayashi T, Suzuki Y, Motoya S, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis—results from a multicenter prospective randomized controlled trial and its post hoc analysis. *J Gastroenterol* 2016. doi: [10.1007/s00535-015-1102-z](https://doi.org/10.1007/s00535-015-1102-z).
 107. Jiang XL, Cui HF, Gao J, Fan H. Low-dose infliximab for induction and maintenance treatment in Chinese patients with moderate to severe active ulcerative colitis. *J Clin Gastroenterol* 2015;49:582–8.
 108. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: Results of a randomised controlled trial. *Gut* 2011. doi: [10.1136/gut.2010.221127](https://doi.org/10.1136/gut.2010.221127).
 109. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014. doi: [10.1053/j.gastro.2013.06.010](https://doi.org/10.1053/j.gastro.2013.06.010).
 110. Sandborn WJ, Van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012. doi: [10.1053/j.gastro.2011.10.032](https://doi.org/10.1053/j.gastro.2011.10.032).
 111. Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. *J Gastroenterol* 2014;49:283–94.
 112. Kirchgessner J, Desai RJ, Beaugerie L, Schneeweiss S, Kim SC. Risk of serious infections with vedolizumab versus tumor necrosis factor antagonists in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2020. doi: [10.1016/j.cgh.2020.12.030](https://doi.org/10.1016/j.cgh.2020.12.030).
 113. Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Editorial: tofacitinib and biologics for moderate-to-severe ulcerative colitis—what is best in class? Authors' reply. *Aliment Pharmacol Ther* 2018;47:540–1.
 114. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. *Clin Gastroenterol Hepatol* 2020. doi: [10.1016/j.cgh.2020.01.008](https://doi.org/10.1016/j.cgh.2020.01.008).
 115. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: The efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015. doi: [10.1111/apt.13083](https://doi.org/10.1111/apt.13083).
 116. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al.; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med* 2019;381:1215–26.
 117. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014;146:392–400.e3.
 118. Targownik LE, Benchimol EI, Bernstein CN, et al. Combined biologic and immunomodulatory therapy is superior to monotherapy for decreasing the risk of inflammatory bowel disease-related complications. *J Crohns Colitis* 2020;14:1354–63.
 119. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019. doi: [10.1016/S2468-1253\(19\)30012-3](https://doi.org/10.1016/S2468-1253(19)30012-3).
 120. Roblin X, Williet N, Boschetti G, et al. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. *Gut* 2020;69:1206–12.
 121. Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol* 2016. doi: [10.1016/j.cgh.2015.06.001](https://doi.org/10.1016/j.cgh.2015.06.001).
 122. Feagan BG, Rutgeerts P, Sands BE, et al.; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.
 123. Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: A Phase 3, randomized, double-blind, placebo-controlled study. *PLoS One* 2019. doi: [10.1371/journal.pone.0212989](https://doi.org/10.1371/journal.pone.0212989).
 124. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012;367:616–24.
 125. Sandborn WJ, Su C, Panes J. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;377:496–7.
 126. Paschos P, Katsoula A, Giouleme O, et al. Tofacitinib for induction of remission in ulcerative colitis: systematic review and meta-analysis. *Ann Gastroenterol* 2018;31:572–82.
 127. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2019. doi: [10.1056/nejmoa1900750](https://doi.org/10.1056/nejmoa1900750).
 128. Janssen Research & Development. *Clinical Study Report Synopsis [Protocol REMICADEUCO3001; Phase 3]*. Xi'an Janssen Pharmaceutical Ltd; 2014.
 129. Ungar B, Mazor Y, Weisshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Aliment Pharmacol Ther* 2016. doi: [10.1111/apt.13631](https://doi.org/10.1111/apt.13631).
 130. Papamichael K, Baert F, Tops S, et al. Post-induction adalimumab concentration is associated with short-term mucosal healing in patients with ulcerative colitis. *J Crohns Colitis* 2017;11:53–9.
 131. Papamichael K, Vande Castele N, Ferrante M, Gils A, Cheifetz AS. Therapeutic drug monitoring during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease: defining a therapeutic drug window. *Inflamm Bowel Dis* 2017;23:1510–5.
 132. Papamichael K, Van Stappen T, Vande Castele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative Colitis. *Clin Gastroenterol Hepatol* 2016;14:543–9.
 133. Gibson DJ, Ward MG, Rentsch C, et al. Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2020;51:612–28.
 134. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology* 2014;147:1296–307.e5.
 135. Ungar B, Kopylov U, Yavzori M, et al. Association of vedolizumab level, anti-drug antibodies, and $\alpha 4\beta 7$ occupancy with response in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2018;16:697–705.e7.
 136. Pouillon L, Rousseau H, Busby-Venner H, et al. Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. *J Crohns Colitis* 2019;13:970–5.
 137. Osterman MT, Rosario M, Lasch K, et al. Vedolizumab exposure levels and clinical outcomes in ulcerative colitis: determining the potential for dose optimisation. *Aliment Pharmacol Ther* 2019;49:408–18.
 138. Adedokun OJ, Xu Z, Marano C, et al. Ustekinumab pharmacokinetics and exposure response in a phase 3 randomized trial of patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2020;18:2244–55.e9.
 139. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response

- to infliximab or adalimumab. *Clin Gastroenterol Hepatol* 2015;13:522–30.e2.
140. Kelly OB, Donnell SO, Stempak JM, Steinhart AH, Silverberg MS. Therapeutic drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. *Inflamm Bowel Dis* 2017;23:1202–9.
 141. Roblin X, Rinaudo M, Del Tedesco E, *et al.* Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol* 2014;109:1250–6.
 142. Colombel JF, Panés J, D’Haens G, *et al.* Higher vs. standard adalimumab maintenance regimens in patients with moderately to severely active ulcerative colitis: Results from the SERENE-UC maintenance study. *J Crohns Colitis* 2020;14[Suppl 1]:S001.
 143. Sandborn WJ, Baert F, Danese S, *et al.* Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020;158:562–72.e12.
 144. Feagan BG, Patel H, Colombel JF, *et al.* Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. *Aliment Pharmacol Ther* 2017. doi: [10.1111/apt.13852](https://doi.org/10.1111/apt.13852).
 145. Wolf D, D’Haens G, Sandborn WJ, *et al.* Escalation to weekly dosing recaptures response in adalimumab-treated patients with moderately to severely active ulcerative colitis. *Aliment Pharmacol Ther* 2014. doi: [10.1111/apt.12863](https://doi.org/10.1111/apt.12863).
 146. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of Janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. *Gastroenterology* 2020;158:1554–73.e12.
 147. Sandborn WJ, Panés J, D’Haens GR, *et al.* Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. *Clin Gastroenterol Hepatol* 2019. doi: [10.1016/j.cgh.2018.11.035](https://doi.org/10.1016/j.cgh.2018.11.035).
 148. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016. doi: [10.1136/annrheumdis-2016-209131](https://doi.org/10.1136/annrheumdis-2016-209131).
 149. Pharmacovigilance Risk Assessment Committee (PRAC). *EMA/631064/2019*. Publisher European Medicines Agency; 2019.
 150. Sandborn WJ, Panés J, Sands BE, *et al.* Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. *Aliment Pharmacol Ther* 2019;50:1068–76.
 151. Vermeire S, Su C, Lawendy N, *et al.* Outcomes of tofacitinib dose reduction in patients with ulcerative colitis in stable remission from the randomised RIVETING Trial. *J Crohns Colitis* 2021;15:1130–41.
 152. European Medicines Agency. *Xeljanz (tofacitinib): Initial Clinical Trial Results of Increased Risk of Major Adverse Cardiovascular Events and Malignancies (Excluding NMSC) with Use of Tofacitinib Relative to TNF-alpha Inhibitors*. https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-xeljanz-tofacitinib-initial-clinical-trial-results_en.pdf Accessed September 27, 2021.
 153. Adamina M, Gerasimidis K, Sigall-Boneh R, *et al.* Perioperative dietary therapy in inflammatory bowel disease. *J Crohns Colitis* 2020;14:431–44.
 154. Torres J, Ellul P, Langhorst J, *et al.* European Crohn’s and Colitis Organisation topical review on complementary medicine and psychotherapy in inflammatory bowel disease. *J Crohns Colitis* 2019;13:673–85e.
 155. Sigall-Boneh R, Levine A, Lomer M, *et al.* Research gaps in diet and nutrition in inflammatory bowel disease. a topical review by D-ECCO Working Group [Dietitians of ECCO]. *J Crohns Colitis* 2017;11:1407–19.
 156. Maaser C, Langholz E, Gordon H, *et al.* European Crohn’s and Colitis Organisation topical review on environmental factors in IBD. *J Crohns Colitis* 2017;11:905–20.
 157. van Rheenen PF, Aloï M, Biron IA, *et al.* European Crohn’s and Colitis Organisation topical review on transitional care in inflammatory bowel disease. *J Crohns Colitis* 2017;11:1032–8.
 158. Sturm A, Maaser C, Mendall M, *et al.* European Crohn’s and Colitis Organisation topical review on IBD in the elderly. *J Crohns Colitis* 2017;11:263–73.
 159. Fiorino G, Lytras T, Younge L, *et al.* Quality of care standards in inflammatory bowel diseases: a European Crohn’s and Colitis Organisation [ECCO] Position Paper. *J Crohns Colitis* 2020;14:1037–48.
 160. Magro F, Doherty G, Peyrin-Biroulet L, *et al.* ECCO position paper: Harmonization of the approach to ulcerative colitis histopathology. *J Crohns Colitis* 2020;14:1503–11.
 161. Danese S, Fiorino G, Raine T, *et al.* ECCO position statement on the use of biosimilars for inflammatory bowel disease—an update. *J Crohns Colitis* 2017;11:26–34.
 162. ECCO. *European Crohn’s Colitis Organisation ECCO e-Guide*. <http://www.e-guide.ecco-ibd.eu>. Accessed 27 October 2021.