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CONSENSUS STATEMENT

Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis: The Toronto Consensus

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See commentary on page 877.

BACKGROUND & AIMS: The medical management of ulcerative colitis (UC) has improved through the development of new therapies and novel approaches that optimize existing drugs. Previous Canadian consensus guidelines addressed the management of severe UC in the hospitalized patient. We now present consensus guidelines for the treatment of ambulatory patients with mild to severe active UC. **METHODS:** A systematic literature search identified studies on the management of UC. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. Statements were developed through an iterative online platform and then finalized and voted on by a working group of specialists. **RESULTS:** The participants concluded that the goal of therapy is complete remission, defined as both symptomatic and endoscopic remission without corticosteroid therapy. The consensus includes 34 statements focused on 5 main drug classes: 5-aminosalicylate (5-ASA), corticosteroids, immunosuppressants, anti–tumor necrosis factor (TNF) therapies, and other therapies. Oral and rectal 5-ASA are recommended first-line therapy for mild to moderate UC, with corticosteroid therapy for those who fail to achieve remission. Patients with moderate to severe UC should undergo a course of oral corticosteroid therapy, with transition to 5-ASA, thiopurine, anti-TNF (with or without thiopurine or methotrexate), or vedolizumab maintenance therapy in those who successfully achieve symptomatic remission. For patients with corticosteroid-resistant/dependent UC, anti-TNF or vedolizumab therapy is recommended. Timely assessments of response and remission are critical to ensuring optimal outcomes. **CONCLUSIONS:** Optimal management of UC requires careful patient assessment, evidence-based use of existing therapies, and thorough assessment to define treatment success.

Keywords: Ulcerative Colitis; 5-Aminosalicylate; Corticosteroid; Thiopurine; Anti–Tumor Necrosis Factor; Vedolizumab; Probiotics.

A substantial burden of illness is attributable to inflammatory bowel disease (IBD)—ulcerative colitis (UC) and Crohn's disease—due to the high prevalence and high per-patient costs of these chronic disorders.[1] The incidence and prevalence of IBD are highest in Western nations, including Canada, the United States, and Europe.[2] There are approximately 104,000 Canadians living with UC and ~10,200 incident cases each year (2012 estimates).[1] In the United States, the prevalence of UC in adults was estimated at 593,000 cases (2009 estimates).[3] In Canada, the total annual cost of IBD was C$2.8 billion (C$1.2 billion in direct costs and C$1.6 billion in indirect costs), corresponding to approximately C$12,000 per year for each patient with IBD (2008 estimates).[1] In the United States, direct medical costs alone are more than $4 billion annually (2004 estimates).[4,5] Furthermore, the personal impact of these disorders includes painful and bothersome symptoms, anxiety regarding the future, and functional impairment.[1] All of these factors are important determinants of health-related quality of life.

In a 2011 survey of Canadian gastroenterologists, topics relevant to IBD were among the most desired educational areas.[6] Four of the top 6 topics were linked to IBD, including difficult cases, therapeutics, pathogenesis and genetics, and nutrition. The management of IBD is complicated by an unpredictable and chronic course, inadequate or delayed access to drug therapies, and a lack of support for patients and caregivers.[1]

The most recent clinical practice guidelines for the medical treatment of ambulatory patients with UC are the second European evidence-based consensus, which incorporates data published until 2012.[7,8] Since that time, therapy has evolved with the approval of new agents (eg, budesonide multi-matrix [MMX], adalimumab, golimumab,

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Abbreviations used in this paper: ADA, antidrug antibodies; CAG, Canadian Association of Gastroenterology; CI, confidence interval; FMT, fecal microbial transplant; GRADE, Grading of Recommendation Assessment, Development and Evaluation; IBD, inflammatory bowel disease; MMX, multi-matrix; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase; UC, ulcerative colitis.

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and vedolizumab) and a better understanding of strategies to optimize anti–tumor necrosis factor (TNF) therapy (eg, measuring anti-TNF trough levels and antibodies). Previous Canadian consensus guidelines addressed the management of severe UC in the hospitalized patient.[9] The purpose of these consensus statements is to review the literature relating to the medical management of UC and to develop specific recommendations for ambulatory patients with mild to severe active UC.

Methods

Scope and Purpose

Specific questions regarding therapy were identified and addressed by the participants, aided by evidence derived from review of the literature on UC. The process for guideline development is outlined in Figure 1. The process took approximately 1 year, with the first meeting of the steering committee in November 2013, the meeting of the full consensus group in June 2014, and submission of the manuscript for publication in November 2014.

Sources and Searches

The editorial office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University conducted a systematic literature search of MEDLINE (1946 on), EMBASE (1980 on), and CENTRAL (Cochrane Central Register of Controlled Trials) up to February 2014. Key search terms were ulcerative colitis, 5-aminosalicylate, corticosteroid, anti–tumor necrosis factor, thiopurine, methotrexate, vedolizumab, and probiotics. The search was limited to human studies and the English language. The MEDLINE, EMBASE, and CENTRAL search strategies used are detailed further in Supplementary Appendix 1. Supplemental manual searches of these databases were performed up to June 2014.

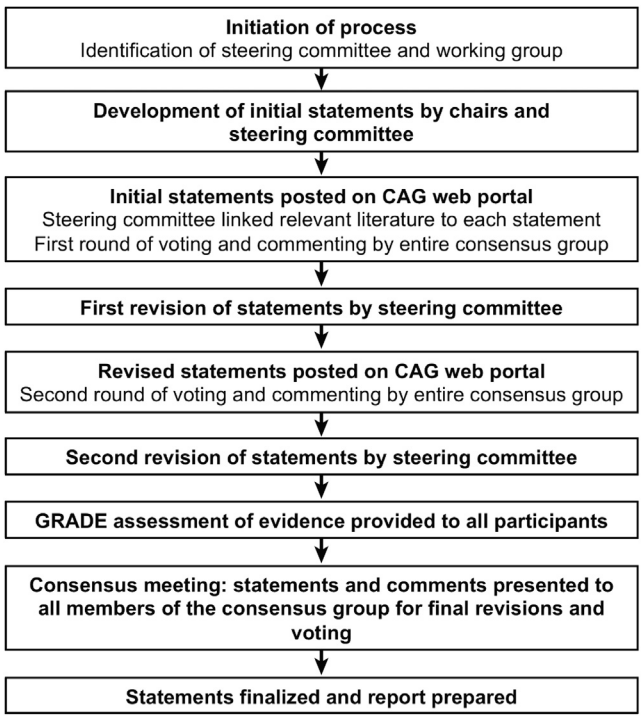

Figure 1. Guideline development process.

Review and Grading of Evidence

The quality of evidence was assessed according to the GRADE (Grading of Recommendation Assessment, Development and Evaluation) approach[10] and determined by 2 methodologists (Dr Grigorios Leontiadis and Dr Francis Tse) who did not vote on the statements. The methodologists determined the risk of bias within individual studies, the risk of bias across studies, and the overall quality of evidence across the identified studies for each statement. The voting members of the consensus group then reviewed and agreed on the GRADE assessments at the meeting.

The quality of evidence for each consensus statement was classified as high, moderate, low, or very low. Evidence from randomized controlled trials (RCTs) was initially classified as high quality but could be downgraded for the following reasons: heterogeneity among outcomes of individual studies, ambiguity in results, indirect study findings, reporting bias, or if it was determined a high risk of bias existed across studies supporting the statement. Data from cohort studies or case-control findings were initially categorized as low-quality evidence; however, the rating could be lowered as a result of the same criteria applied to RCTs, or raised if a very large treatment effect or a dose-response relationship was identified or if all plausible biases would tend to change the magnitude of effect toward the opposite direction.[10]

Approved product labeling from government regulatory agencies varies from country to country, and while not ignored, recommendations are based on evidence from the literature and consensus discussion and may not fully reflect the product labeling for a given country.

Consensus Process

The consensus group included 23 voting participants, including academic and community gastroenterologists with expertise in various aspects of UC management, a pharmacist, and a nonvoting facilitator (Dr Paul Moayyedi).

Working subgroups and the meeting cochairs (Dr Brian Bressler and Dr John K. Marshall) developed initial statements. A web-based consensus platform (ECD Marketing Solutions, Atlanta, GA) supported by the Canadian Association of Gastroenterology (CAG) was used to facilitate most aspects of the consensus process before the final face-to-face meeting. Via the consensus platform, the working groups (1) reviewed the results of initial literature searches and identified relevant references that were then "tagged" (selected and linked) to each statement, (2) used a modified Delphi process[11,12] to vote anonymously on their level of agreement with the statements, (3) suggested revisions to statements, and (4) provided comments on specific references and background data. Statements were revised through 2 separate iterations and finalized at the consensus meeting. All participants had access to all abstracts and electronic copies of the individual "tagged" references. The GRADE evaluations of the evidence for each statement were provided at the meeting.

The group held a 2-day consensus conference in Toronto, Ontario, Canada, in June 2014, at which data were presented, the wording of the statements was discussed and finalized, and

participants voted on their level of agreement with each statement. A statement was accepted if >75% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1 to 5 (with 1, 2, and 3 indicating disagree strongly, disagree, and uncertain, respectively). The strength of each recommendation was assigned by the consensus group, per the GRADE system, as strong ("we recommend...") or weak ("we suggest..."). The strength of recommendations is composed of 4 components (risk/benefit balance, patients' values and preferences, cost and resource allocation, and quality of evidence). Therefore, it is possible for a recommendation to be classified as strong despite having low-quality evidence to support it or as weak despite the existence of high-quality evidence to support it.[13] Based on the GRADE approach, a strong recommendation indicates the statement should be applied in most cases, whereas a weak recommendation signifies that clinicians "…should recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her or his values and preferences."[13]

The manuscript was initially drafted by Drs Bressler and Marshall and then reviewed and revised by members of the steering committee before being circulated to all participants for review and approval. Written disclosures of potential conflicts of interest for the 24-month period preceding the consensus meeting were completed and submitted in accordance with CAG policies and were subsequently available to all members of the consensus group.

Role of the Funding Sources

The consensus meeting was funded by unrestricted grants to the CAG from AbbVie Canada, Actavis Specialty Pharmaceuticals, Janssen Inc, Shire Pharma Canada ULC, Takeda Canada, and the Canadian Institutes of Health Research. The CAG administered all aspects of the meeting, and the funding sources had no role in drafting or approving these guidelines.

Definitions of UC

Before finalizing the individual statements for the management of UC, the consensus group first discussed and agreed on definitions of terminology that were then used throughout the consensus process. Definitions were presented by a member of the steering committee (C.N.B.), discussed and revised, and then agreed on by the group without a formal vote.

Disease Extent

The extent of endoscopic disease was categorized as (1) proctitis (distal to the rectosigmoid junction or within 18 cm of the anal verge), (2) left-sided colitis (extending anywhere from the sigmoid to the splenic flexure), or (3) extensive colitis (extending beyond the splenic flexure).[14]

Disease Activity

Although the participants concluded that disease activity is best determined by clinical symptoms and an objective assessment of disease activity through endoscopy, they also recognized that, for pragmatic reasons, it is often necessary to make clinical decisions based on symptoms alone. For the purposes of these guidelines, disease activity reflects symptomatic assessment unless otherwise stated. Specific categories of disease activity were defined as mild, moderate, and severe active disease.

The consensus group recommended that, ideally, a formal scoring tool such as the Mayo score or a similar disease activity score should be used to determine disease activity in patients with UC. The Mayo score includes 4 measures: stool frequency, rectal bleeding, endoscopic findings, and the physician's global assessment (Supplementary Appendix 2).[15] Unless otherwise specified, references to mild, moderate, and severe disease activity in this document refer to those disease strata as defined by Mayo score. Although such a scoring system is desirable for accurate and consistent assessment of disease activity, it is often necessary to make management decisions in the absence of endoscopic information while considering the subjective aspects of disease presentation not captured by the full Mayo score. In such circumstances, the partial Mayo score (which omits the endoscopic subscore) can be informative.

Remission and Response

Terminology and definitions used in this guideline are shown in Table 1. Complete remission, including both symptomatic and endoscopic remission, is the preferred outcome. Complete remission requires endoscopy to document mucosal healing. Although this cannot be conducted at every assessment, the consensus group recommended performance of endoscopy when making important management decisions, such as assessing efficacy at the end of induction therapy or considering a change in therapy due to loss of response. Mucosal healing is an important predictor of long-term outcomes of treatment for UC. Patients who achieve mucosal healing (generally defined as a Mayo endoscopic subscore of 0 or 1) have lower rates of hospitalization, decreased need for corticosteroids, and lower rates of colectomy.[16–18]

However, it should be recognized that escalation of therapy to treat patients who are asymptomatic but have endoscopically active disease remains controversial.

Table 1. Defining Remission and Response in Patients With UC

Complete remission	Both symptomatic remission and endoscopic healing as defined below
Endoscopic healing	Normal mucosa, vascular blurring, or chronic changes (eg, inflammatory polyps, scarring) without friability
Symptomatic remission	Normal stool frequency (≤3/day) and no blood in the stool
Symptomatic response	Meaningful improvement in symptoms as judged by both the patient and physician in the absence of remission; response should not be considered a desirable final outcome but is useful to assess early response to treatment

Similarly, the management of histological disease activity with macroscopic endoscopic remission is also unclear.[19]

In lieu of full endoscopic assessment, objective measures of inflammation may be useful when evaluating disease activity. Fecal calprotectin levels have been shown to correlate with endoscopic disease activity better than either symptoms or systemic inflammatory markers such as C-reactive protein.[20]

Risk Profile

Individual patients may present with similar disease activity but differ in their risk profile for adverse outcomes; this concept should be considered when making therapeutic decisions. Risk factors for colectomy include more extensive colitis,[21] flares requiring hospitalization,[22,23] and elevated levels of acute phase reactants, such as a high erythrocyte sedimentation rate[21] or high concentration of C-reactive protein.[24,25] Older age has been associated with a lower risk of relapse or disease progression[23,26] and colectomy.[21] Patients who require corticosteroid therapy are at higher risk for both relapse[27,28] and colectomy.[29]

Disease Impact

The overall impact of disease ("severity") has not typically been defined or captured in clinical trials. The consensus group believed it is important for clinicians to consider more than symptoms when managing UC and proposed a more holistic approach to assessing the impact of UC on patients' lives (Table 2). Disease impact can help inform a physician's global assessment, which is a component of the Mayo score and other disease activity scoring tools.

Use of Corticosteroids

Based on clinical experience and various definitions used in clinical trials of UC, the consensus group defined "corticosteroid resistance" as a lack of a symptomatic response despite a course of oral prednisone of 40 to 60 mg/day (or equivalent)[25] for a minimum of 14 days. "Corticosteroid dependence" was defined as the inability to withdraw (within 3 months of initiation) oral corticosteroid therapy without recurrence of symptoms, a symptomatic relapse within 3 months of stopping corticosteroid therapy, or the need for 2 or more courses of corticosteroid therapy within 1 year.

Treatment Failure

Definitions of treatment failure are shown in Table 3. Before determining treatment failure, clinicians should rule out other causes of symptoms, such as malignancy, irritable bowel syndrome, bleeding hemorrhoids, dietary intolerance, drug toxicity, or enteric infection (eg, *Clostridium difficile* or cytomegalovirus), as the circumstances warrant.[7]

Table 2. Factors to Consider in a Comprehensive Assessment of Disease Impact

High disease activity (in acute setting)
Frequency of hospitalization
Need for surgery
Inability to work or participate in leisure activities
Failure to respond to medication

Recommendation Statements

The individual recommendation statements are provided and include the "GRADE" of supporting evidence and the voting results, after which a discussion of the evidence considered for the specific statement is presented. A summary of the recommendation statements is provided in Table 4.

Statements Regarding 5-Aminosalicylates

Statement 1. In patients with mild to moderate active ulcerative proctitis, we recommend rectal 5-aminosalicylate (5-ASA), at a dosage of 1 g daily, as first-line therapy to induce symptomatic remission. *GRADE: Strong recommendation, high-quality evidence. Vote: strongly agree, 57%; agree, 30%; uncertain, 9%; disagree, 4%.*

Statement 2. In patients with mild to moderate active left-sided UC, we recommend 5-ASA enemas, at a dosage of at least 1 g daily, as an alternative first-line therapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 52%; agree, 48%.*

Meta-analyses have shown the efficacy of rectally administered 5-ASA as induction therapy in patients with mild to moderate active ulcerative proctitis or left-sided UC.[30–36] A meta-analysis of 38 studies in patients with mild to moderate active UC included 10 studies of rectal 5-ASA versus placebo.[30] Rectal 5-ASA was superior to placebo, with a pooled odds ratio (OR) for symptomatic remission of 8.30 (8 trials; 95% confidence interval [CI], 4.28–16.12; $P < .00001$) and for endoscopic remission of 5.31 (7 trials; 95% CI, 3.15–8.92; $P < .00001$). Rectal 5-ASA was also superior to rectal corticosteroids for inducing symptomatic remission, with a pooled OR of 1.65 (6 trials; 95% CI, 1.11–2.45; $P = .01$). In these RCTs, 5-ASA was delivered as liquid, gel, or foam enemas or suppositories in doses ranging from 1 to 4 g, with no difference in treatment

Table 3. Definitions of Treatment Failure

5-ASA failure	Inability of the patient to achieve and maintain complete corticosteroid-free remission despite optimal treatment with oral, rectal, or combination 5-ASA therapy
Thiopurine failure	Inability of the patient to maintain corticosteroid-free complete remission despite dose optimization
Biologic failure	Primary failure: Inability of the patient to achieve corticosteroid-free complete remission despite dose optimization
	Secondary failure: Inability of the patient to maintain corticosteroid-free complete remission after achieving a symptomatic response

Table 4. Summary of Consensus Recommendations for the Medical Management of UC

Statements regarding 5-ASA

1. In patients with mild to moderate active ulcerative proctitis, we recommend rectal 5-ASA, at a dosage of 1 g daily, as first-line therapy to induce symptomatic remission. *GRADE: Strong recommendation, high-quality evidence.*
2. In patients with mild to moderate active left-sided UC, we recommend 5-ASA enemas, at a dosage of at least 1 g daily, as an alternative first-line therapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence.*
3. In patients with mild to moderate active UC of any disease extent beyond proctitis, we recommend an oral 5-ASA preparation, at dosages between 2.0 and 4.8 g/day, as an alternative first-line therapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence.*
4. In patients with mild to moderate active UC of any disease extent beyond proctitis, we suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone as an alternative first-line therapy to induce complete remission. *GRADE: Weak recommendation, low-quality evidence.*
5. We recommend that patients with UC be evaluated for lack of symptomatic response to oral/rectal 5-ASA induction therapy in 4 to 8 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, very low-quality evidence.*
6. In patients with oral or rectal 5-ASA–induced complete remission of mild to moderate active left-sided UC or proctitis, we recommend the same therapy be continued to maintain complete remission. *GRADE: Strong recommendation, moderate-quality evidence.*
7. In patients with oral 5-ASA–induced complete remission of mild to moderate active UC of any disease extent, we recommend continued oral therapy of at least 2 g/day to maintain complete remission. *GRADE: Strong recommendation, moderate-quality evidence.*
8. In selected 5-ASA–naive patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest an oral 5-ASA preparation of at least 2 g/day while being assessed for corticosteroid-free complete remission. *GRADE: Weak recommendation, very low-quality evidence.*
9. In patients with UC who have failed to respond to oral 5-ASA, we recommend against switching to another oral 5-ASA formulation to induce remission. *GRADE: Strong recommendation, low-quality evidence.*
10. When using oral 5-ASA to induce or maintain complete remission of UC, we suggest once-daily over more frequent dosing. *GRADE: Weak recommendation, moderate-quality evidence.*

Statements regarding corticosteroids

11. In patients with moderate to severe active UC, we recommend oral corticosteroids as first-line therapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence.*
12. In patients with mild to moderate active UC who fail to respond to 5-ASA therapy, we recommend oral corticosteroids as second-line therapy to induce complete remission. *GRADE: Strong recommendation, low-quality evidence.*
13. In patients with mild to moderate active left-sided UC or proctitis who fail to respond to rectal 5-ASA therapy, we suggest rectal corticosteroids as second-line therapy to induce complete remission. *GRADE: Weak recommendation, overall very low-quality evidence.*
14. In patients with UC, we recommend against the use of oral corticosteroids to maintain complete remission because they are ineffective for this indication and their prolonged use is associated with significant adverse effects. *GRADE: Strong recommendation, moderate-quality evidence.*
15. In patients with mild to moderate UC of any disease extent, we suggest oral budesonide MMX as an alternative first-line therapy to induce complete remission. *GRADE: Weak recommendation, high-quality evidence.*
16. We recommend that patients with UC be evaluated for lack of symptomatic response to corticosteroid induction therapy within 2 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, very low-quality evidence.*

Statements regarding immunosuppressants

17. In patients with UC, we recommend against the use of thiopurine monotherapy to induce complete remission. *GRADE: Strong recommendation, low-quality evidence.*
18. In selected patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest thiopurine monotherapy as an option to maintain complete corticosteroid-free remission. *GRADE: Weak recommendation, low-quality evidence.*
19. In patients with UC, we recommend against the use of methotrexate monotherapy to induce or maintain complete remission. *GRADE: Strong recommendation, low-quality evidence for induction and very low-quality evidence for maintenance.*

Statements regarding anti-TNF therapy

20. In patients with UC who fail to respond to thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, high-quality evidence.*
21. When starting anti-TNF therapy, we recommend it be combined with a thiopurine or methotrexate rather than used as monotherapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence for azathioprine and very low-quality evidence for methotrexate.*
22. In patients with UC who are corticosteroid dependent, we recommend anti-TNF therapy to induce and maintain complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence.*
23. We recommend that patients with UC be evaluated for lack of symptomatic response to anti-TNF induction therapy in 8 to 12 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, low-quality evidence.*
24. In patients with UC who respond to anti-TNF induction therapy, we recommend continued anti-TNF therapy to maintain complete remission. *GRADE: Strong recommendation, very low-quality evidence for infliximab and adalimumab and high-quality evidence for golimumab.*
25. In patients with UC who have a suboptimal response to anti-TNF induction therapy, we recommend dose intensification to achieve complete remission. *GRADE: Strong recommendation, very low-quality evidence.*
26. In patients with UC who lose response to anti-TNF maintenance therapy, we recommend optimizing dose to recapture complete remission. *GRADE: Strong recommendation, very low-quality evidence.*

Table 4. Continued

27. We recommend that dose optimization for patients with UC be informed by therapeutic drug monitoring. *GRADE: Strong recommendation, low-quality evidence.*

Statements regarding other agents

28. In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence.*
29. In patients with secondary failure to an anti-TNF therapy, we recommend switching to another anti-TNF therapy or vedolizumab based on therapeutic drug monitoring results to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence.*
30. In patients with moderate to severe active UC who fail to respond to corticosteroids, thiopurines, or anti-TNF therapies, we recommend vedolizumab to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, moderate-quality evidence.*
31. We recommend that patients with UC be evaluated for lack of symptomatic response to vedolizumab induction therapy in 8 to 14 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, very low-quality evidence.*
32. In patients with UC who respond to vedolizumab, we recommend continued vedolizumab therapy to maintain complete corticosteroid-free remission. *GRADE: Strong recommendation, moderate-quality evidence.*
33. In patients with UC, we recommend against fecal microbial transplant to induce or maintain complete remission outside the setting of a clinical trial. *GRADE: Strong recommendation, low-quality evidence.*
34. In patients with UC, we recommend against probiotics to induce or maintain complete remission outside the setting of a clinical trial. *GRADE: Strong recommendation, very low-quality evidence.*

NOTE. The strength of each recommendation was assigned by the consensus group, per the GRADE system, as strong ("we recommend…") or weak ("we suggest…"). A recommendation could be classified as strong despite low-quality evidence to support it or as weak despite the existence of high-quality evidence due to the 4 components that are considered in each recommendation (risk/benefit balance, patients' values and preferences, cost and resource allocation, and quality of evidence).

response according to dose or formulation. Meta-analyses of 4 studies of rectal 5-ASA compared with oral 5-ASA have not shown superiority for symptomatic improvement (pooled OR, 2.25; 95% CI, 0.53–9.54; $P = .27$)[30] or relative risk (RR) of no remission (0.82; 95% CI, 0.52–1.28).[31]

Three trials included in the meta-analysis by Marshall et al (2010) enrolled only patients with proctitis, but rectal 5-ASA appeared to be effective in both proctitis and left-sided disease.[30] One trial reported that rectal 5-ASA was more effective than oral 5-ASA alone for proctitis.[37] One additional RCT published after the meta-analysis evaluated 5-ASA suppositories according to disease extent.[38] For proctitis, the endoscopic remission rates after 4 weeks were 83.8% and 36.1% in the 5-ASA and placebo suppository groups, respectively, and for all other types of UC were 78.6% and 21.4%, respectively ($P < .0001$ for both subgroups). The consensus group concluded that rectal 5-ASA (any formulation) is an effective therapy for both proctitis and proctosigmoiditis.

Complete remission should be the goal of therapy in most patients. However, because the natural history of proctitis includes a low risk of colectomy[23] and cancer,[39] it may be less important to confirm mucosal healing in these patients, and symptomatic assessments may be adequate.

For proctitis, no dose response has been shown for total daily doses greater than 1 g. Suppositories may be more appropriate than enemas in patients with proctitis, because their distribution mirrors disease extent.[40] For active left-sided UC, 5-ASA enemas at a dosage of at least 1 g daily are preferred over 5-ASA suppository therapy because they are more likely to deliver medication to the splenic flexure.[41] An RCT found that low-volume 5-ASA enemas were as effective as high-volume 5-ASA enemas but were better tolerated in patients with distal UC.[42]

Statement 3. In patients with mild to moderate active UC of any disease extent beyond proctitis, we recommend an oral 5-ASA preparation, at dosages between 2.0 and 4.8 g/day, as an alternative first-line therapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 52%; agree, 43%; uncertain, 4%.*

Meta-analyses support the efficacy of oral 5-ASA for induction therapy for patients with mild to moderate active UC.[43,44] Results were similar in these meta-analyses, reported as the RR of no remission; one meta-analysis of 8 trials found an RR of 0.86 (95% CI, 0.81–0.91),[43] and another analysis of 11 trials found an RR of 0.79 (95% CI, 0.73–0.85).[44]

Overall, in the meta-analyses, a dose response was reported,[43] with dosages $\geq$2.0 g/day shown to be more effective than dosages $<$2.0 g/day for remission (RR, 0.91; 95% CI, 0.85–0.98).[44] However, data are conflicting for dosages $>$2 g/day; a pooled analysis of the ASCEND trials (n = 1459 patients) found no statistically significant difference in clinical improvement between mesalamine (Asacol, Procter & Gamble Pharmaceuticals, Inc, Mason, OH) 4.8 g/day and 2.4 g/day,[45–47] although subgroup analysis indicated that patients with moderate disease may benefit from the higher dosage.[43] In contrast, studies with mesalamine (Pentasa, Shire US Inc, Wayne, PA) and MMX mesalamine (Lialda, Shire US Inc or Mezavant, Shire Pharma Canada ULC, Saint-Laurent, QC, Canada) have reported no statistically significant differences in efficacy with 4.0 to 4.8 g/day versus 2.25 to 2.4 g/day.[43] The consensus group recommended a dosage of 2.0 to 2.4 g/day for patients with mild UC, whereas patients with moderate disease may benefit from higher doses. The consensus group agreed that sulfasalazine has efficacy similar to that of 5-ASA but that

higher total doses of sulfasalazine are required to deliver equivalent doses of 5-ASA.

Intolerance of 5-ASA occurs in up to 15% of patients; the most common adverse events are flatulence, abdominal pain, nausea, diarrhea, headache, worsening UC, rash, and thrombocytopenia.[7,43] Meta-analyses report no significant differences in the incidence of adverse events between 5-ASA and placebo.[43,48] However, sulfasalazine is not as well tolerated as 5-ASA.[43] There have been rare, idiosyncratic reports of renal impairment,[49] and the product labeling recommends that all patients have an evaluation of renal function before initiation of therapy and periodically thereafter while on 5-ASA therapy. The consensus group believed there was no evidence that patients with a history of allergy to acetylsalicylic acid could not safely take 5-ASA preparations. The majority of patients who are intolerant or hypersensitive to sulfasalazine can take 5-ASA preparations without risk of similar reactions, but caution should be exercised.

Statement 4. In patients with mild to moderate active UC of any disease extent beyond proctitis, we suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone as an alternative first-line therapy to induce complete remission. *GRADE: Weak recommendation, low-quality evidence. Vote: strongly agree, 43%; agree, 57%.*

A meta-analysis of 4 RCTs in patients with active UC reported that combination rectal and oral therapy was superior to oral 5-ASA alone for induction of remission (RR of no remission, 0.65; 95% CI, 0.47–0.91).[31] There are few data comparing the efficacy of combination therapy with rectal 5-ASA alone.

In the meta-analysis, there was no significant difference in the rate of adverse events between patients receiving combination (22.3%) and oral 5-ASAs (26.9%) (RR, 0.77; 95% CI, 0.55–1.09).[31]

Given the limited evidence showing the superiority of this strategy, patient preference and cost should be considered when choosing combination therapy over oral 5-ASA monotherapy; however, the consensus group concluded that combination therapy is the optimal first-line option given a potentially favorable risk/benefit trade-off.

Statement 5. We recommend that patients with UC be evaluated for lack of symptomatic response to oral/rectal 5-ASA induction therapy in 4 to 8 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 35%; agree, 57%; uncertain, 4%; disagree, 4%.*

The RCTs of 5-ASA therapy report that approximately 10% to 30% of patients were in symptomatic remission at week 2, 30% to 45% at week 4, and 45% to 50% at week 8.[50,51] The median time to symptomatic remission was 10 to 37 days with oral 5-ASA.[50,51] Generally, 5-ASA therapy is associated with improvements in symptom scores over the first 2 to 4 weeks, although additional improvement can occur up to week 16.[50,52–57]

The consensus group considered that symptomatic improvement should be evident by week 4 and symptomatic remission achieved by week 12. Although it is important not to delay assessment of therapeutic response and risk poor outcomes from the continuation of ineffective treatment, it is also important not to evaluate and change therapies before the completion of an adequate trial. However, definite and progressive worsening before the full 4- to 8-week trial may require intervention.

Statement 6. In patients with oral or rectal 5-ASA–induced complete remission of mild to moderate active left-sided UC or proctitis, we recommend the same therapy be continued to maintain complete remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 48%; agree, 52%.*

Almost three-fourths of patients with left-sided UC or proctitis will experience a relapse within 1 year, underscoring the importance of maintenance therapy.[58,59] Meta-analyses have shown the efficacy of maintenance 5-ASA therapy in these patients.[32,58,59] In an analysis of 7 RCTs in patients treated with 5-ASA for a mean of 6 to 24 months, maintenance rectal 5-ASA therapy was associated with an RR of relapse of 0.60 (95% CI, 0.49–0.73; number needed to treat, 3) compared with placebo.[58] A second meta-analysis, using different definitions of remission, included only 4 RCTs.[59] In these studies, 12-month symptomatic remission rates were 62% with rectal 5-ASA and 30% with placebo (RR, 2.22; 95% CI, 1.26–3.90; $P < .01$). A meta-analysis of 2 RCTs found no statistically significant differences between rectal and oral 5-ASA for either symptomatic or endoscopic remission over a 6-month follow-up period.[59]

In the meta-analysis by Ford et al (2012), a subgroup analysis of continuous (daily) and intermittent (first 7 days of the month, twice weekly, every third day) dosing schedules found a trend toward better results with the continuous dosing schedule, but this was not significant.[58] Therefore, rectal 5-ASA therapy can be used at a similar or reduced dosing frequency as the induction therapy to maintain complete remission. The consensus group agreed that not all patients with proctitis require maintenance therapy. In addition, patient preference should be considered.

Meta-analyses of maintenance studies have reported no significant differences in rates of adverse events between 5-ASA and placebo groups.[58,59]

Statement 7. In patients with oral 5-ASA–induced complete remission of mild to moderate active UC of any disease extent, we recommend continued oral therapy of at least 2 g/day to maintain complete remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 57%; agree, 43%.*

Relapse rates among patients with UC of any extent were approximately 60% in the placebo arms of RCTs; thus, maintenance therapy is recommended.[44,60] A meta-analysis of 11 RCTs in patients with quiescent UC found an RR of relapse with 5-ASA of 0.65 (95% CI, 0.55–0.76; number needed to treat, 4) compared with placebo.[44] An analysis of 6 RCTs that assessed complete remission (clinical and endoscopic) showed an RR of 0.59 (95% CI, 0.52–0.68). A meta-analysis of 7 trials (excluding sulfasalazine) reported relapse rates of 41% with 5-ASA compared with 58% with placebo (RR, 0.69; 95% CI, 0.62–0.77).[60] Sulfasalazine was statistically significantly superior to 5-ASA, with relapse

rates of 48% and 43%, respectively (12 studies; RR, 1.14; 95% CI, 1.03–1.27).[60]

Dosages of 5-ASA of ≥2.0 g/day appear to be more effective than <2.0 g/day for preventing relapse (RR, 0.79; 95% CI, 0.64–0.97).[44,60] High-dose therapy appears to be as safe as low-dose therapy and is not associated with a higher incidence of adverse events.[60] The consensus group concluded that patients with more active UC, extensive colitis, or frequent relapses may benefit in particular from a higher maintenance dosage up to 4.8 g/day.

No significant differences in rates of adverse events between oral 5-ASA and placebo have been reported.[44,60]

Statement 8. In selected 5-ASA–naive patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest an oral 5-ASA preparation of at least 2 g/day while being assessed for corticosteroid-free complete remission. *GRADE: Weak recommendation, very low-quality evidence. Vote: strongly agree, 9%; agree, 78%; uncertain, 13%.*

Meta-analyses have confirmed the benefits of 5-ASA maintenance therapy (as described in statements 5 and 7); however, in most studies, patients were not stratified according to the treatment used to induce remission.[44,60] A subgroup analysis of one RCT found no differences in the efficacy of 5-ASA for maintenance of remission between patients who had or had not received prior oral corticosteroid therapy.[61]

Data suggest that the need for corticosteroid treatment is a marker of poor prognosis.[27–29] Therefore, the consensus group considered that 5-ASA maintenance therapy after corticosteroid induction therapy is a reasonable option for select patients, such as those with newly diagnosed lower-risk UC not previously treated with 5-ASA. For patients at higher risk for relapse or colectomy (see Definitions), immunosuppressants may be preferred (see statement 16). Other factors to consider include patient preference, cost, and the appropriateness of the corticosteroid induction therapy.

Statement 9. In patients with UC who have failed to respond to oral 5-ASA, we recommend against switching to another oral 5-ASA formulation to induce complete remission. *GRADE: Strong recommendation, low-quality evidence. Vote: strongly agree, 39%; agree, 57%; uncertain, 4%.*

Meta-analyses have reported no clinically important differences in efficacy or safety among the various 5-ASA formulations for induction or maintenance therapy.[60,62] The consensus group believed that for patients who fail to achieve remission with 5-ASA therapy, there appears to be little or no benefit to changing among 5-ASA formulations before moving on to other therapeutic options. However, this recommendation does not preclude switching 5-ASA formulations for other reasons, such as adherence, tablet size, perceived intolerance, or cost.

Statement 10. When using oral 5-ASA to induce or maintain complete remission of UC, we suggest once-daily over more frequent dosing. *GRADE: Weak recommendation, moderate-quality evidence. Vote: strongly agree, 52%; agree, 43%; uncertain, 4%.*

A meta-analysis of 3 trials found no statistically significant differences in efficacy or adherence between once-daily and conventionally dosed 5-ASA for induction of remission (nonremission RR, 0.95; 95% CI, 0.82–1.10).[43,63] One additional RCT also found no differences in rates of remission or safety between once- and twice-daily oral 5-ASA (with once-daily enema).[64] For maintenance of remission, meta-analyses of 7 RCTs[60,63,65] showed no significant difference in relapse rates with once-daily compared with conventional 5-ASA dosing (RR, 0.94; 95% CI, 0.82–1.08).[65] In one RCT, which showed superior maintenance of remission with oral 5-ASA dosed once versus twice daily, it was speculated that higher absolute topical drug concentrations may have resulted in better pharmacological control of inflammation; however, there are no data to support this.[66] Once-daily dosing was not associated with a significant increase in the rate of adverse events compared with conventional dosing.[43,60,63,65]

There were no significant differences in rates of medication adherence between once-daily and conventional dosing.[43,60,63,65] However, adherence in the clinical trial environment is considerably higher (90%)[63] than in community-based studies (40%).[67] Nonadherence with maintenance therapy is associated with a greater risk of recurrence and higher health care costs.[68–70] In addition, data suggest that most patients prefer once-daily over conventional dosing.[71,72]

The consensus group suggested once-daily dosing of 5-ASA therapy, which may enhance adherence in clinical practice, particularly during maintenance therapy.

Statements Regarding Corticosteroids

Statement 11. In patients with moderate to severe active UC, we recommend oral corticosteroids as first-line therapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 70%; agree, 30%.*

Statement 12. In patients with mild to moderate active UC who fail to respond to 5-ASA therapy, we recommend oral corticosteroids as second-line therapy to induce complete remission. *GRADE: Strong recommendation, low-quality evidence. Vote: strongly agree, 57%; agree, 43%.*

A meta-analysis of 5 RCTs showed that corticosteroids were superior to placebo for induction of remission (RR of no remission, 0.65; 95% CI, 0.45–0.93).[73] The analysis did not specify whether the patients were treatment naive or previously treated (ie, first- or second-line oral corticosteroid therapy). The optimal dose and dosing regimen for systemic corticosteroids in UC is uncertain, but based on a meta-analysis reporting no evidence of benefit with dosages higher than 60 mg/day, the consensus group agreed with the commonly used regimen of oral prednisone 40 to 60 mg/day (or equivalent).[25] Oral corticosteroid preparations with low systemic bioavailability, such as beclomethasone dipropionate or budesonide (MMX), have also shown efficacy for induction of remission with fewer systemic corticosteroid adverse effects.[74,75]

Approximately 50% of patients experience short-term corticosteroid-related adverse events such as acne, edema,

sleep and mood disturbance, glucose intolerance, and dyspepsia.[76,77]

The consensus group agreed that selected patients, such as those with contraindications to corticosteroids, can be considered for anti-TNF or vedolizumab therapy (see statements 20 and 30). Because oral corticosteroids are not recommended for maintenance therapy (see statement 14), appropriate assessments for maintenance therapy should be considered when corticosteroid therapy is initiated (eg, thiopurine methyltransferase [TPMT] testing if thiopurines are being considered, hepatitis B and tuberculosis testing if anti-TNF therapy is being considered; see statements 18 and 22).

Statement 13. In patients with mild to moderate active left-sided UC or proctitis who fail to respond to rectal 5-ASA therapy, we suggest rectal corticosteroids as second-line therapy to induce complete remission. *GRADE: Weak recommendation, overall very low-quality evidence. Vote: strongly agree, 26%; agree, 61%; uncertain, 13%.*

A meta-analysis that included studies of both conventional corticosteroids (2 RCTs) and budesonide (2 RCTs) showed that rectal corticosteroid therapy was superior to placebo in inducing remission.[78] In a meta-analysis of 6 RCTs, rectal 5-ASA was superior to rectal corticosteroids for inducing symptomatic remission with an OR of 1.65 (95% CI, 1.11–2.45; $P = .01$).[30] An analysis performed for this consensus included only the 3 trials using conventional corticosteroids[53,79,80] and found 2-fold higher odds of remission with 5-ASA (OR, 2.01; 95% CI, 1.41–2.88; $P = .0001$) (Figure 2). The nonsystemic corticosteroid budesonide has also been shown to be inferior to 5-ASA for induction of remission.[54,55,78] A meta-analysis of 4 RCTs with rectal beclomethasone dipropionate showed no significant difference in improvement/remission compared with 5-ASA (OR, 1.23; 95% CI, 0.82–1.85; $P =$ not significant [NS]).[36]

Despite evidence showing the superiority of rectal 5-ASA over rectal corticosteroids, the consensus group agreed that there is a role for rectal corticosteroids as second-line therapy given their superiority over placebo. Furthermore, hydrocortisone and budesonide are available as foam preparations,[81,82] which can have an advantage over liquid formulations when proctitis is quite active.

Rectal corticosteroids are associated with similar short-term adverse events as seen with oral corticosteroids, although generally at lower frequency and severity.[78]Although the consensus group suggested rectal corticosteroid therapy, they also believed there may be a role for adding oral 5-ASA in patients who fail to respond to rectal 5-ASA (particularly for patients with moderate left-sided UC) (see statement 4).

Statement 14. In patients with UC, we recommend against the use of oral corticosteroids to maintain complete remission because they are ineffective for this indication and their prolonged use is associated with significant adverse effects. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 96%; uncertain, 4%.*

Few RCTs have assessed the efficacy of corticosteroids for maintenance therapy,[76,83–85] although 2 small RCTs have found this strategy to be ineffective.[84,85] Adverse effects associated with long-term use of corticosteroids include cataracts, osteoporosis, myopathy, and susceptibility to infections.[76,77,86] In the TREAT registry of patients with Crohn's disease, prednisone therapy was associated with an increased risk of serious infections (hazard ratio, 1.57; 95% CI, 1.17–2.10; $P = .002$) and increased mortality (hazard ratio, 2.14; 95% CI, 1.55–2.95; $P < .001$).[87] The consensus group recommended against the use of oral corticosteroids for maintenance therapy because evidence suggests that the risks of long-term therapy outweigh the benefits.

Statement 15. In patients with mild to moderate UC of any disease extent, we suggest oral budesonide MMX as an alternative first-line therapy to induce complete remission. *GRADE: Weak recommendation, high-quality evidence. Vote: strongly agree, 35%; agree, 61%; uncertain, 4%.*

In RCTs, budesonide in the oral MMX formulation was significantly more effective than placebo[75,88,89] and as effective as 5-ASA in inducing remission.[88] However, this may not be true of other budesonide formulations; the ileal-release preparations of budesonide, Entocort (AstraZeneca, Lund Sweden) and Budenofalk (Dr Falk Pharma GmbH, Freiburg, Germany), were inferior to placebo[90] and 5-ASA,[91] respectively.[92]

Budesonide has been associated with a lower rate of systemic adverse effects than conventional corticosteroids (33% vs 55%).[77] Budesonide has not been associated with suppression of plasma cortisol[90] or a significant decrease in bone mineral density.[93]

Although budesonide MMX is not approved in Canada, it is available in other jurisdictions. The consensus group agreed that budesonide MMX might be appropriate both as an alternative to 5-ASA as first-line therapy and as second-line therapy in patients with mild to moderate UC who fail to respond to or do not tolerate 5-ASA.

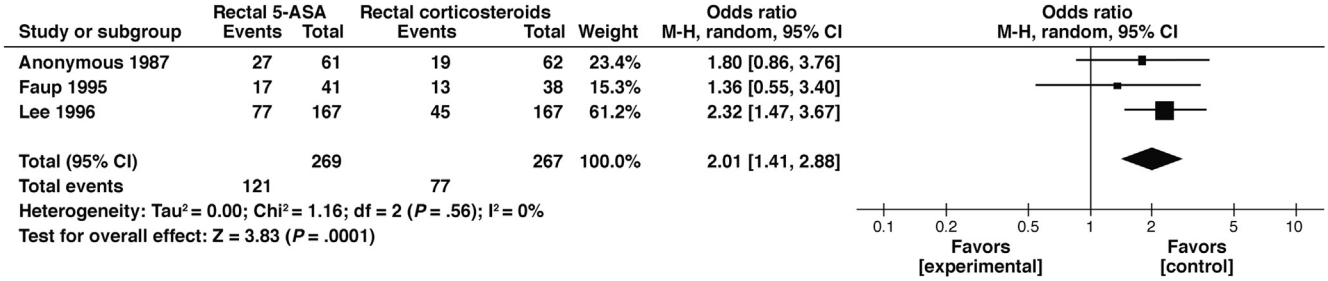

Figure 2. Meta-analysis of rectal corticosteroids versus 5-ASA controls for induction of symptomatic remission.

Statement 16. We recommend that patients with UC be evaluated for lack of symptomatic response to corticosteroid induction therapy within 2 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 65%; agree, 35%.*

Patients undergoing a course of oral corticosteroid induction therapy should be assessed within 2 weeks. In trials, significant improvements in clinical and endoscopic measures with corticosteroid therapy are seen at the earliest assessment (week 2) compared with baseline.[55,74] Early clinical assessment to identify nonresponders can help avoid delays in initiating other effective therapy. In addition, the short-term and long-term adverse event profiles associated with corticosteroid use suggest minimizing exposure whenever possible.[76,77]

The consensus group agreed that if there is no response within 2 weeks, therapy should be modified; however, if there is a partial response, a short extension of full-dose corticosteroid induction therapy may be warranted based on a patient's individual situation.

Statements Regarding Immunosuppressants

Statement 17. In patients with UC, we recommend against the use of thiopurine monotherapy to induce complete remission. *GRADE: Strong recommendation, low-quality evidence. Vote: strongly agree, 52%; agree, 43%; uncertain, 4%.*

A meta-analysis of 4 controlled trials concluded that the thiopurines, azathioprine and 6-mercaptopurine, were not effective for the induction of remission in patients with UC (OR, 1.59; 95% CI, 0.59–4.29; P = NS) compared with placebo or 5-ASA therapy.[94] Analysis of the 2 placebo-controlled RCTs[95,96] found no significant benefit of azathioprine/6-mercaptopurine for the outcome of endoscopic remission (RR, 0.85; 95% CI, 0.71–1.01)[97] or clinical remission (OR, 1.44; 95% CI, 0.68–3.03; P = NS).[94] One RCT showed that azathioprine was significantly more effective than 5-ASA in inducing complete, corticosteroid-free remission in patients with corticosteroid-dependent UC (OR, 4.78; 95% CI, 1.57–14.5; P = .006).[98]

Given the safety and tolerability issues (see statement 18) and delayed onset of action (up to 2–6 months for therapeutic effect),[94] the consensus group recommended against the routine use of these agents for induction therapy. However, thiopurines could be considered in select patients with mild UC who are uncontrolled on 5-ASA but refuse anti-TNF therapy when the prolonged time to therapeutic effect is unlikely to result in significant deterioration in disease severity. It is also important to recognize that thiopurines can be combined with anti-TNF therapies to augment their efficacy as both induction and maintenance agents (see statement 21).

Statement 18. In selected patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest thiopurine monotherapy as an option to maintain complete corticosteroid-free remission. *GRADE: Weak recommendation, low-quality evidence. Vote: strongly agree, 22%; agree, 78%.*

Meta-analyses support the benefit of azathioprine for maintenance of remission[94,97,99] in patients with UC. A meta-analysis of 4 RCTs,[95,96,100,101] found that 44% of azathioprine-treated patients failed to maintain remission compared with 65% of patients receiving placebo (RR, 0.68; 95% CI, 0.54–0.86).[99] Similar results were found in a meta-analysis of 3 studies (RR, 0.60; 95% CI, 0.37–0.95),[97] which did not include the withdrawal study by Hawthorne et al (1992).[101] Two of these studies included patients in remission after corticosteroid therapy,[95,100] while one included corticosteroid-dependent patients.[96] The withdrawal study included patients in remission on azathioprine and found 1-year relapse rates of 36% with continued azathioprine and 59% with placebo (hazard ratio, 0.5; 95% CI, 0.25–1.0; P = .039).[101] The quality of the individual studies used in these meta-analyses was insufficient due to heterogeneous trial designs, small patient numbers, and variability of outcome measures; therefore, the consensus group suggested, rather than recommended, this approach.

Although rare, thiopurine therapy is associated with an increased risk of lymphoma (including hepatosplenic T-cell lymphoma)[102–104] and nonmelanoma skin cancer.[105] In 2014, Health Canada issued an alert warning of the risk of hepatosplenic T-cell lymphoma with azathioprine/6-mercaptopurine.[106] Thiopurines have also been associated with bone marrow suppression, pancreatitis, hepatotoxicity, allergic reactions, and opportunistic infections, especially when used in combination with corticosteroids or infliximab.[7,102] A position statement from the CAG recommended that continuation of thiopurine therapy balance the evidence for risk and efficacy against an individual patient's response to therapy, preferences, and risk tolerance.[107]

Because thiopurines are metabolized by TPMT, which may be absent or present in low levels in some patients, a TPMT assay is necessary before initiation of treatment to identify patients at risk for severe dose-dependent myelosuppression.[102] In addition, higher levels of the thiopurine metabolite 6-thioguanine nucleotide have been correlated with clinical remission rates; therefore, thiopurine metabolite levels may be helpful to guide therapy.[102] Note that TPMT testing does not replace the need for mandatory monitoring of complete blood cell count.

Given the safety and tolerability issues, the consensus group suggested thiopurine maintenance therapy for selected patients, including patients with a low risk of disease progression who responded to their first course of corticosteroids and those who cannot afford or are unable to tolerate anti-TNF therapy. The consensus group believed that for patients who are corticosteroid dependent and thus at higher risk of poorer outcomes, more effective, safer options were preferred over thiopurine therapy (see statement 22). Response to a thiopurine for corticosteroid-sparing maintenance therapy should be evaluated as early as 10 to 12 weeks.[96,100]

Statement 19. In patients with UC, we recommend against the use of methotrexate monotherapy to induce or maintain complete remission. *GRADE: Strong recommendation, low-quality evidence for induction and very low-quality evidence for maintenance. Vote: strongly agree, 65%; agree, 26%; uncertain, 9%.*

Meta-analyses of methotrexate for induction[97,108] or maintenance therapy[97,109] reveal the paucity of data with this agent for the treatment of UC. The only placebo-controlled RCT for induction therapy reported no statistically significant benefit of methotrexate (RR, 1.29; 95% CI, 0.95–1.75) over placebo in patients with corticosteroid-dependent UC.[110] A meta-analysis of 2 RCTs[110,111] found no statistically significant benefit of adjunctive methotrexate over placebo for maintenance of remission (RR, 0.59; 95% CI, 0.04–7.90).[97]

In corticosteroid-dependent patients, 2 small RCTs with active comparator arms[112,113] and 2 cohort studies[114,115] found that approximately 20% to 60% of patients achieved corticosteroid-free remission, which was not significantly different from that seen with 5-ASA.[112]

Two multicenter randomized trials, METEOR (European) and MERIT (US), comparing methotrexate and placebo are under way. These trials should help determine if methotrexate is a valuable therapeutic option in UC.

Based on current data, the consensus group recommended against the routine use of methotrexate for induction or maintenance therapy.

Statements Regarding Anti-TNF Therapy

Statement 20. In patients with UC who fail to respond to thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, high-quality evidence. Vote: strongly agree, 70%; agree, 30%.*

The anti-TNF therapies, infliximab, adalimumab, and golimumab, have shown efficacy for the induction and maintenance of remission in patients with moderate to severe active UC. The efficacy of infliximab was shown in meta-analyses of RCTs in patients who failed to respond to or were receiving corticosteroids.[116–118] A meta-analysis of 5 trials found that infliximab was superior to placebo in inducing endoscopic remission (RR for no remission, 0.72; 95% CI, 0.57–0.91; $P = .006$) (Figure 3).[116] Analysis of the 2 largest trials, the ACT 1 (n = 364) and ACT 2 (n = 364) trials,[119] found that infliximab was more effective than placebo in inducing clinical (RR, 3.22; 95% CI, 2.18–4.76) and endoscopic remission (RR, 1.88; 95% CI, 1.54–2.28).[117]

Two large RCTs, ULTRA 1 (n = 390)[120] and ULTRA 2 (n = 494),[121] have assessed the efficacy of adalimumab in patients with moderate to severe active UC failing to respond to treatment with corticosteroids or immunosuppressants. A meta-analysis of these 2 trials conducted for this consensus showed that adalimumab was effective in inducing complete remission (OR for no remission, 0.60; 95% CI, 0.42–0.86; $P = .006$) (Figure 4).

The efficacy of golimumab was shown in the PURSUIT-SC trial (n = 774), with rates of complete remission of 18% with golimumab compared with 6% with placebo ($P < .0001$).[122]

The consensus group concluded that no data exist to guide the choice of a particular anti-TNF therapy. Comparison of data from different studies is not appropriate, and head-to-head comparative studies are not available.

In induction trials, the rates of adverse events with anti-TNF therapy, including infusion/injection reactions, headache, rash, and arthralgia, were not significantly different from placebo.[116] However, adverse events related to sensitization may be more common with prolonged use. Anti-TNF therapy is associated with a small increased absolute risk of opportunistic infections[123] and serious infections,[124] which is discussed in more detail in statement 24.

Statement 21. When starting anti-TNF therapy, we recommend it be combined with a thiopurine or methotrexate rather than used as monotherapy to induce complete remission. *GRADE: Strong recommendation, moderate-quality evidence for azathioprine and very low-quality evidence for methotrexate. Vote: strongly agree, 26%; agree, 65%; uncertain, 9%.*

The use of combination therapy is based on the rationale that immunosuppressants optimize induction and may reduce the likelihood of secondary loss of response to anti-TNF therapies. Across therapeutic areas in which anti-TNF therapies have been used, the development of anti-drug antibodies (ADA) has been associated with poorer clinical outcomes, and the use of immunosuppressants with thiopurines or methotrexate has been shown to reduce their formation.[125] Furthermore, adalimumab levels were found

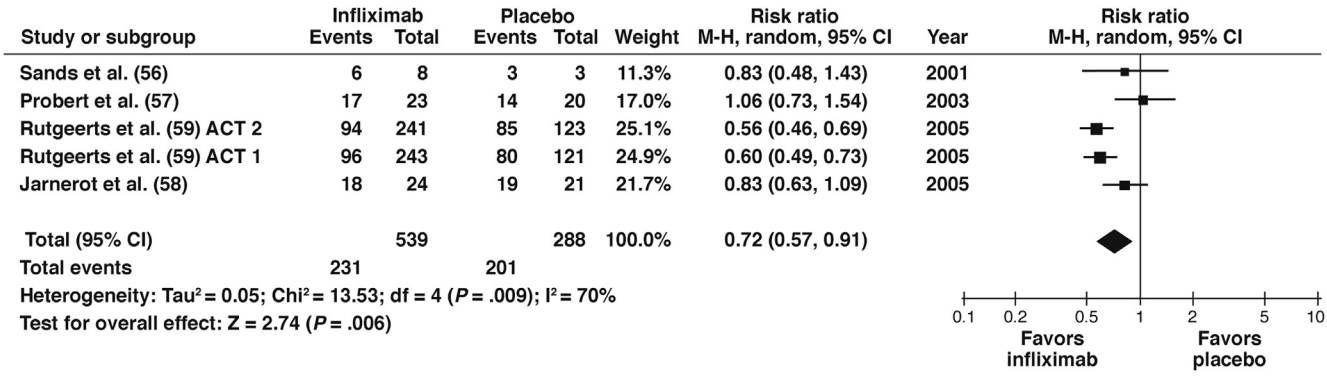

Figure 3. Meta-analysis of infliximab for induction of endoscopic remission (RR for no remission). From Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:644–659.[116] Copyright ©2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

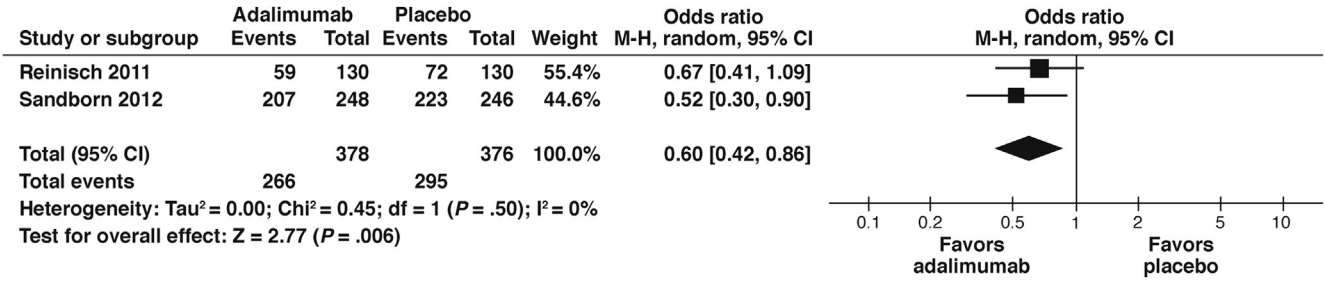

Figure 4. Meta-analysis of adalimumab for induction of complete remission.

to be significantly higher in patients with rheumatoid arthritis receiving concomitant methotrexate.[126]

The data from RCTs regarding the use of anti-TNF therapies and azathioprine in combination are sparse, and no such data exist for combination therapy with methotrexate. The efficacy of anti-TNF therapy in combination with azathioprine is supported by the results of the UC SUCCESS trial[127] and observational data.[120,121,128] Among anti-TNF–naive patients with moderate to severe UC included in the UC SUCCESS trial, corticosteroid-free remission rates at 16 weeks were significantly higher with the combination of infliximab plus azathioprine (39.7%) compared with either infliximab (22.1%, $P = .017$) or azathioprine monotherapy (23.7%; $P = .032$).[127] Combination therapy also led to significantly better mucosal healing than azathioprine monotherapy. However, the UC-SUCCESS trial was only of 16 weeks' duration, and other end points, including mucosal healing and improvements in partial or total Mayo scores, were similar between the infliximab monotherapy and combination groups.

In addition, a systematic review of subgroup data from 4 RCTs concluded that concomitant use of immunosuppressants did not improve efficacy or pharmacokinetics in patients with IBD receiving maintenance infliximab.[129] Nonetheless, these data should be interpreted with caution and in the context of the recent experience in Crohn's disease, where a similar conclusion based on subgroup analyses was later discredited by the results of SONIC.[130]

Analysis of patients receiving immunosuppressants in the adalimumab study, ULTRA 1, showed a more pronounced treatment effect in patients treated with immunosuppressants without corticosteroids at baseline.[120] In ULTRA 2, there was a lower rate of development of adalimumab ADAs in patients receiving combination therapy compared with adalimumab monotherapy.[121] In the PURSUIT studies, concomitant immunosuppressant use was associated with a decreased incidence of antibodies to golimumab but did not substantially affect golimumab serum levels or improve efficacy.[128]

Although the absolute baseline rates of serious infections and malignancy are low among patients with IBD, they may be increased with anti-TNF therapies and thiopurines, particularly when these agents are used in combination (see statements 18 and 24).[124,129] An analysis of patients with Crohn's disease found an increased risk of nonmelanoma skin cancer or other cancers in patients receiving combination therapy but not in those receiving anti-TNF monotherapy, suggesting that the increased rate of malignancy compared with the general population is likely due to the immunosuppressant rather than the anti-TNF therapy.[131] However, the magnitude of the increased risk remains controversial.

Although controversial, and based on somewhat limited evidence, the consensus group concluded that combination therapy is preferred in thiopurine-naive patients starting anti-TNF therapy. The decision as to what to do in patients who fail to respond to thiopurine therapy is less clear. Available data for combination therapy in patients with UC is primarily based on the use of azathioprine and infliximab.[127] However, the observational data suggesting a decreased risk of developing anti-TNF antibodies to adalimumab and golimumab provide support for the relevance of this strategy for all 3 of the anti-TNF therapies. In addition, data extrapolated from studies in patients with rheumatoid arthritis[126] led the consensus group to believe that methotrexate may also be a useful alternative to azathioprine in some patients at higher risk for nonmelanoma skin cancer or lymphoma, such as elderly patients.

Statement 22. In patients with UC who are corticosteroid dependent, we recommend anti-TNF therapy to induce and maintain complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 52%; agree, 48%.*

Patients who require corticosteroid therapy are at higher risk for relapse[27,28] and colectomy.[29] Given the adverse effects associated with long-term corticosteroid use,[76,77,86] one of the most important goals of therapy in UC is to maintain corticosteroid-free remission.

A majority of patients in RCTs of anti-TNF therapies in UC had failed to respond to or were receiving corticosteroid therapy.[116,120–122] Anti-TNF therapy showed corticosteroid-sparing effects in these trials. In the ACT 1 and 2 trials with infliximab, approximately 60% of patients were receiving corticosteroids at baseline, and approximately 30% had corticosteroid-resistant disease.[119] Significantly more patients had corticosteroid-free complete remission in the infliximab groups compared with placebo (20%–30% vs 3%–10% at week 30). In addition, complete remission rates were similar in patients who were and were not corticosteroid resistant.

In the ULTRA 2 study, approximately 31% of patients in the adalimumab group and 18% in the placebo group discontinued corticosteroid therapy by week 16, and this was maintained through week 52.[121] In the PURSUIT maintenance study, 54% of patients were receiving corticosteroids

at baseline; of these, approximately one-fourth achieved corticosteroid-free complete remission at week 54 with golimumab compared with 18% with placebo (not statistically significant).[132]

Although azathioprine is also recommended as an option in patients who have achieved symptomatic remission on oral corticosteroids (see statement 18), the consensus group believed that anti-TNF combination therapy is the preferred choice for corticosteroid-dependent patients because of the more robust evidence for efficacy and the suggestion of potentially better short-term mucosal healing rates with infliximab compared with azathioprine in the UC SUCCESS trial.[127]

Statement 23. We recommend that patients with UC be evaluated for lack of symptomatic response to anti-TNF induction therapy in 8 to 12 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, low-quality evidence. Vote: strongly agree, 43%; agree, 57%.*

Most RCTs assessed patients every 2 weeks and reported significant improvements in symptom scores as early as week 2 to 4 with anti-TNF therapies compared with placebo.[120–122] In the anti-TNF induction therapy trials, significantly greater remission rates with anti-TNF therapy compared with placebo were seen at week 8.[119–122] In addition, in ULTRA 2, the proportion of patients achieving symptomatic remission with adalimumab reached a maximum at week 16 and declined thereafter.[121]

Therefore, the consensus group agreed that clinical assessment at 8 to 12 weeks after initiation of therapy is important to identify patients who have failed to respond and modify their therapy. If a response occurs, subsequent assessments should include endoscopy to confirm complete remission, but the optimal timing of endoscopy is currently uncertain. Patients with more severe disease may require earlier assessments.

Statement 24. In patients with UC who respond to anti-TNF induction therapy, we recommend continued anti-TNF therapy to maintain complete remission. *GRADE: Strong recommendation, very low-quality evidence for infliximab and adalimumab and high-quality evidence for golimumab. Vote: strongly agree, 65%; agree, 35%.*

The efficacy of infliximab therapy after 1 year was shown in the ACT 1 trial, with 35% of patients achieving complete remission compared with 16% receiving placebo ($P = .001$).[119] Longer-term open-label follow-up of infliximab-treated patients showed that approximately 90% of patients maintained symptomatic remission with up to 3 years of therapy.[133] Similarly, adalimumab was effective in the 1-year ULTRA 2 trial, with 31% of the patients who had a clinical response at week 8 achieving complete remission by week 52.[134] In the open-label follow-up of patients in the ULTRA 1 study, 30% were in complete remission at 1 year, including almost 40% of patients who had responded at week 8.[135]

In the 1-year PURSUIT maintenance study, patients who had responded to golimumab induction therapy were randomized to maintenance therapy with golimumab or placebo.[132] At week 54, patients who received golimumab were more likely to be in complete remission (23%–28%) than patients assigned to placebo (15.6%; $P = .004$).

Anti-TNF therapies have been associated with a small increased risk of opportunistic infections, particularly when used in combination with corticosteroids or immunosuppressants[123,124,136]; however, the absolute risk remains low. A meta-analysis of 22 RCTs in patients with UC and Crohn's disease reported opportunistic infections in 0.9% (39/4135) of patients receiving anti-TNF therapies compared with 0.3% (9/2919) of patients receiving placebo (RR, 2.05; 95% CI, 1.10–3.85).[123] In the anti-TNF therapy group, infections included *Mycobacterium tuberculosis* (n = 8), herpes simplex infection (n = 8), oral or esophageal candidiasis (n = 6), herpes zoster infection (n = 6), varicella-zoster virus infection (n = 2), cytomegalovirus or Epstein–Barr virus infection (n = 2), and *Nocardia* infection (n = 1). Anti-TNF therapy was associated with a 2.5-fold increased risk of tuberculosis infection.

A meta-analysis of 22 RCTs in patients with UC and Crohn's disease reported malignancies in 0.39% (16/4135) of patients receiving anti-TNF therapies compared with 0.45% (13/2919) of patients receiving placebo (RR, 0.77; 95% CI, 0.37–1.59).[136] There were no cases of lymphoma with anti-TNF therapy compared with 3 (0.1%) with placebo. Anti-TNF therapy did not appear to be associated with an increased risk of malignancy in trials of up to 1 year.

The evidence grading is higher for golimumab,[132] which used a rerandomization design for maintenance, compared with adalimumab and infliximab,[119,133–135] which used continuous treatment designs and thus were not true assessments of maintenance therapy contingent on successful induction. However, although the level of evidence may differ, the consensus group determined that there was no evidence to suggest clinical differences among the agents, and therapy should continue with the agent used to induce remission. There are few data beyond 1 year for most agents; therefore, the consensus group recommended that anti-TNF therapy be continued until loss of response. Patients should be informed of the potential safety issues, particularly when anti-TNF therapies are used in combination with corticosteroids or immunosuppressants.

Statement 25. In patients with UC who have a suboptimal response to anti-TNF induction therapy, we recommend dose intensification to achieve complete remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 39%; agree, 61%.*

Statement 26. In patients with UC who lose response to anti-TNF maintenance therapy, we recommend optimizing dose to recapture complete remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 61%; agree, 39%.*

In patients with an inadequate response to initial anti-TNF therapy, it is important to consider dose intensification before deciding this to be a primary biologic failure. In RCTs, patients with higher serum anti-TNF concentrations have a higher probability of induction and maintenance of complete remission.[128,137,138] Higher trough levels have been associated with higher rates of mucosal healing.[139,140] During induction therapy, dose intensification can include increasing the dose or shortening the interval between doses.

During maintenance therapy, a secondary loss of response may be the result of inadequate drug levels, which may, in some cases, reflect the development of ADAs.[133,141] A retrospective analysis found that among 110 patients undergoing serum concentration testing because of loss of response or partial response, subtherapeutic concentrations were seen in 45% and ADAs in 17%.[142] In patients with subtherapeutic anti-TNF therapy concentrations, dose escalation was associated with a response in 86% of patients, whereas in antibody-positive patients, dose escalation had a response of only 17%. Similarly, in a prospective study of consecutive patients with IBD having a disease flare while on adalimumab maintenance therapy, dose optimization led to symptomatic response in 67% of patients with low adalimumab trough levels without ADAs but therapeutic failure in those with both low adalimumab levels and ADAs.[143]

In an open-label study of patients with Crohn's disease with loss of response to infliximab, shortening the treatment interval from 8 to 4 weeks resulted in symptomatic responses in 83% of patients at week 54. A correlation between clinical efficacy and serum trough level was found ($P < 0.01$, overall).[140]

The consensus group concluded that doses of anti-TNF therapy should be optimized before considering anti-TNF therapy to be a failure. Ideally, this should be informed by therapeutic drug monitoring, but this is not universally available (see statement 27).

Statement 27. We recommend that dose optimization for patients with UC be informed by therapeutic drug monitoring. *GRADE: Strong recommendation, low-quality evidence. Vote: strongly agree, 61%; agree, 35%; uncertain, 4%.*

The negative impact of low serum trough levels[128,137–140] and ADAs on outcomes[141,143] suggests the value of therapeutic drug monitoring in guiding management decisions. Therapeutic drug monitoring should include measurement of both the trough level of anti-TNF therapy and the titer of ADAs.

In RCTs of anti-TNF maintenance therapy, approximately 3% of patients developed anti-golimumab antibodies during 1-year follow-up,[132] and approximately 15% of patients tested positive for antibodies to infliximab during up to 3 years of therapy.[133] Among patients with secondary loss of response to anti-TNF therapy, approximately 20% will test positive for ADAs.[142,143] Although ADAs may be transient and may not always lead to a worse clinical outcome, sustained high-titer ADA levels lead to permanent loss of response.[141]

A study of consecutive patients with IBD and secondary failure to infliximab maintenance therapy used therapeutic drug monitoring to show that an increase in infliximab trough level after dose intensification strongly predicted the likelihood of achieving mucosal healing.[144] A retrospective analysis of therapeutic drug monitoring in patients with partial response or loss of response showed that a dose increase was more effective than switching anti-TNF therapies when trough levels were low, but changing to another anti-TNF therapy was more effective when antibodies were detected.[142] Conversely, in a prospective cohort study of patients with secondary biologic failure, the presence of high trough levels was associated with failure of 2 anti-TNF therapies in 90% of patients.[143]

The consensus group considered that therapeutic drug monitoring should be used (when available) to guide treatment decisions, particularly for secondary loss of response.

Statements Regarding Other Agents

Statement 28. In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 43%; uncertain, 9%.*

Statement 29. In patients with secondary failure to an anti-TNF therapy, we recommend switching to another anti-TNF therapy or vedolizumab based on therapeutic drug monitoring results to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 43%; agree, 57%.*

Statement 30. In patients with moderate to severe active UC who fail to respond to corticosteroids, thiopurines, or anti-TNF therapies, we recommend vedolizumab to induce complete corticosteroid-free remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 70%; agree, 26%; disagree, 4%.*

For patients with an inadequate response to anti-TNF therapy, dose intensification should first be considered (see statements 25 and 26). Ideally, this should be informed by therapeutic drug monitoring (see statement 25).

In patients with biologic failure despite dose intensification, no studies have directly compared switching to vedolizumab and switching to an alternate anti-TNF therapy. The available observational data suggest that switching to a different anti-TNF therapy may be more effective in patients who develop ADAs and less effective in primary failure (see statements 25, 26, and 27).[139,142,143]

Because vedolizumab acts via a different mechanism than anti-TNF therapies, it is possible that switching to this class of agents may be effective in patients with either primary or secondary anti-TNF therapy failure.

In the induction component of the GEMINI I trial, 374 randomized patients who had previously received therapy with corticosteroids, immunosuppressants, or anti-TNF therapies were randomized to vedolizumab or placebo.[145] At week 6, vedolizumab showed significantly higher rates of complete remission compared with placebo in patients overall (16.9% vs 5.4%; $P = .001$) and numerically higher rates in patients with prior anti-TNF therapy (9.8% vs 3.2%), corticosteroid (21.4% vs 0%), or immunosuppressant failure (21.9% vs 10.9%).[145,146] Rates of symptomatic response were significantly higher in the overall patient population (47.1% vs 25.5%; $P < .001$) and those with prior anti-TNF therapy (39.0% vs 20.6%) or corticosteroid failure (59.5% vs 20.0%).[146] In patients with prior corticosteroid

failure, mucosal healing rates were dramatically improved with vedolizumab therapy compared with placebo (59.5% vs 24.0%). An earlier, small phase 2 dose-finding RCT found that symptomatic response rates with vedolizumab were approximately twice those of placebo (>50% vs 22%–33%).[147]

During the induction phase, the proportion of patients experiencing one or more adverse events was similar between the active treatment and placebo groups (40% vs 46%), and the rate of serious adverse events was lower with vedolizumab (2% vs 7%).[145] The most common adverse events reported with vedolizumab were headache, worsening disease activity, and infection.

The consensus group concluded that vedolizumab is a useful option in patients who have failed to respond to corticosteroid, immunosuppressant, or anti-TNF therapy. No data are currently available regarding treatment strategies following failure of vedolizumab; however, a trial of anti-TNF therapy can be considered. The GEMINI I trial showed no significant differences in efficacy between 4-week and 8-week maintenance dosing but did show an exposure-response relationship.[145] Patients assigned to 4-week dosing did not experience more adverse events than those who received treatment every 8 weeks. However in the absence of controlled data, dose intensification to 4-week dosing is not advocated. For patients who are unresponsive to induction with all medical therapies, or those with prolonged corticosteroid dependence, colectomy remains an option.[7,9]

Statement 31. We recommend that patients with UC be evaluated for lack of symptomatic response to vedolizumab induction therapy in 8 to 14 weeks to determine the need to modify therapy. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 35%; agree, 65%.*

In the GEMINI I trial, vedolizumab showed significantly greater symptomatic response compared with placebo at week 6 (47.1% vs 25.5%; 95% CI, 11.6–31.7; $P < .001$).[145] Improvements in mean partial Mayo scores seemed to reach a maximum at week 6 and were maintained throughout the maintenance phase of the trial with little further improvement.

The consensus group believed that in clinical practice, initial follow-up should occur before the first maintenance dose and thus recommended that symptomatic response be assessed at 8 to 14 weeks. This recommendation does not preclude earlier assessments, particularly for tolerability, if clinically indicated.

Statement 32. In patients with UC who respond to vedolizumab, we recommend continued vedolizumab therapy to maintain complete corticosteroid-free remission. *GRADE: Strong recommendation, moderate-quality evidence. Vote: strongly agree, 87%; agree, 13%.*

In the maintenance phase of the GEMINI I trial, patients who responded to blinded or open-label vedolizumab therapy (n = 373) were randomized to continued vedolizumab every 4 or every 8 weeks or placebo. At week 52, vedolizumab showed significantly higher rates of complete remission compared with placebo in patients in the overall group (44.8% and 41.8% vs 15.9%; $P < .001$). In patients who had failed to respond to corticosteroids, long-term mucosal healing rates were significantly higher with vedolizumab compared with placebo (60.0% and 68.4% vs 26.9%).[146] No difference in efficacy was observed between dosing every 4 and every 8 weeks.[145]

In another small trial, vedolizumab was effective in maintaining complete remission in approximately 60% of patients treated with 8-week doses for up to 78 weeks. No new safety signals were observed during longer-term therapy.[148]

Analysis of safety findings from 9 clinical trials that included both patients with IBD and healthy controls (n = 579) showed vedolizumab to be well tolerated.[149] The proportion of patients experiencing one or more adverse events was similar between the active treatment and placebo groups (84% vs 87%), as was the rate of serious adverse events (12% vs 14%). The most common adverse events reported with vedolizumab were headache, nausea, abdominal pain, fatigue, and nasopharyngitis.[149] As of February 2013, no cases of progressive multifocal leukoencephalopathy had been reported in approximately 3000 patients exposed to vedolizumab for a median of 18.8 months.[145] In the GEMINI I trial, serious infections were not more common with vedolizumab than with placebo.[145]

Among 620 patients, 3.7% of patients had at least one blood sample that was positive for anti-vedolizumab antibodies, and 1% had persistent anti-vedolizumab antibodies through week 52. Anti-vedolizumab antibodies were detected in 10% of patients when measured at week 66 (after the drug was no longer in the patient's system).[150] The use of concomitant immunosuppressant therapy was associated with decreased immunogenicity. Based on these data and experience with other monoclonal antibodies, the consensus group believed that combination immunosuppressant therapy should be considered when using vedolizumab.

Based on favorable 1-year efficacy and safety data, the consensus group recommended ongoing maintenance therapy in patients who respond to induction with vedolizumab.

Statement 33. In patients with UC, we recommend against fecal microbial transplant to induce or maintain complete remission outside the setting of a clinical trial. *GRADE: Strong recommendation, low-quality evidence. Vote: strongly agree, 70%; agree, 30%.*

Data are insufficient to support the use of fecal microbial transplant (FMT) in patients with UC. Although case reports have suggested benefits,[151] interim analysis of the first RCT of FMT in 63 patients with active UC found no significant benefits of FMT at week 7.[152] Some patients reported subjective improvement, and with continued therapy to 12 weeks, 33% of patients achieved complete remission.

A CAG position paper on the use of FMT recommended that in the absence of controlled data showing clear efficacy, FMT should be used for the treatment of UC only in the clinical trial setting.[151] Until the results of ongoing clinical trials with FMT available, the consensus group recommends against its use in clinical practice.

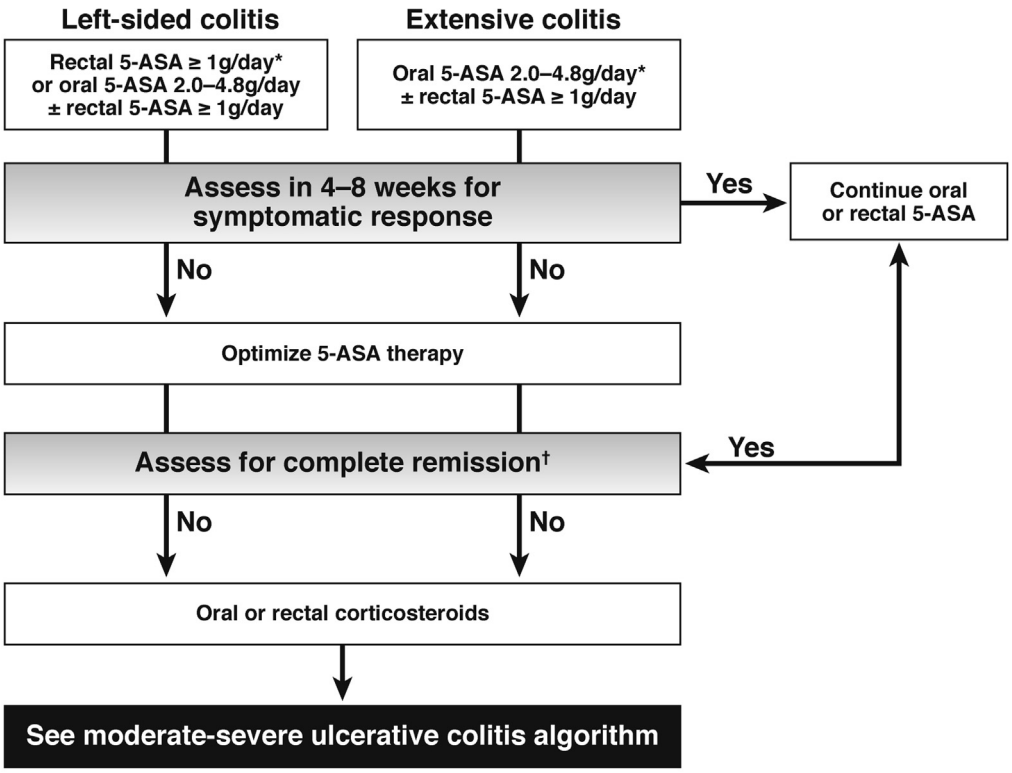

Figure 5. Consensus-guided algorithm for the management of mild to moderate active UC. *Where available, oral MMX budesonide is an alternative. †The optimal time to assess for complete remission is uncertain but is between 4 and 12 months after initiation of therapy.

Statement 34. In patients with UC, we recommend against probiotics to induce or maintain complete remission outside the setting of a clinical trial. *GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 43%; uncertain, 9%.*

A meta-analysis of 23 RCTs showed that probiotics, primarily as an adjunct to 5-ASA or immunosuppressant therapy, significantly increased the rate of remission in patients with UC (RR, 1.80; $P < .0001$).[153] The beneficial effect seems to be apparent with VSL#3 only.[153,154]

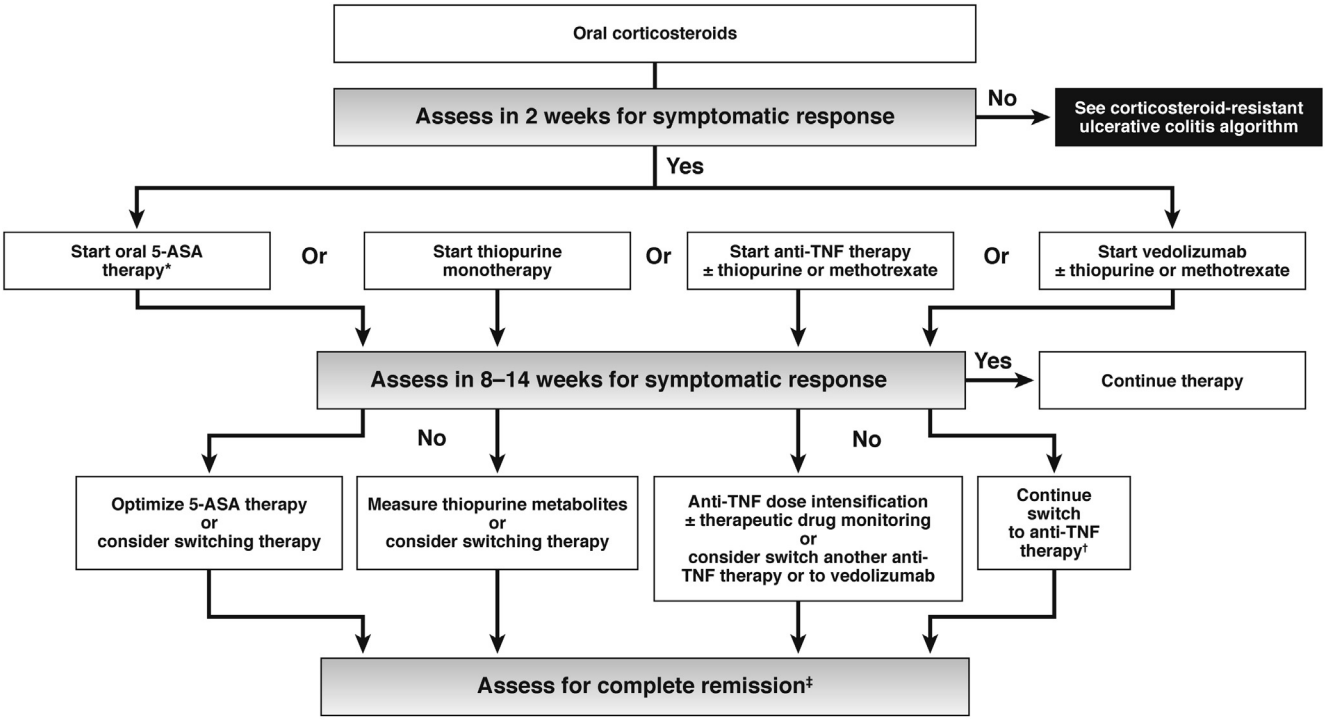

Figure 6. Consensus-guided algorithm for the management of moderate to severe active UC. *Not appropriate for patients who fail to respond to 5-ASA. †The role of dose intensification and therapeutic drug monitoring with vedolizumab therapy is uncertain. ‡The optimal time to assess for complete remission is uncertain but is between 4 and 12 months after initiation of therapy.

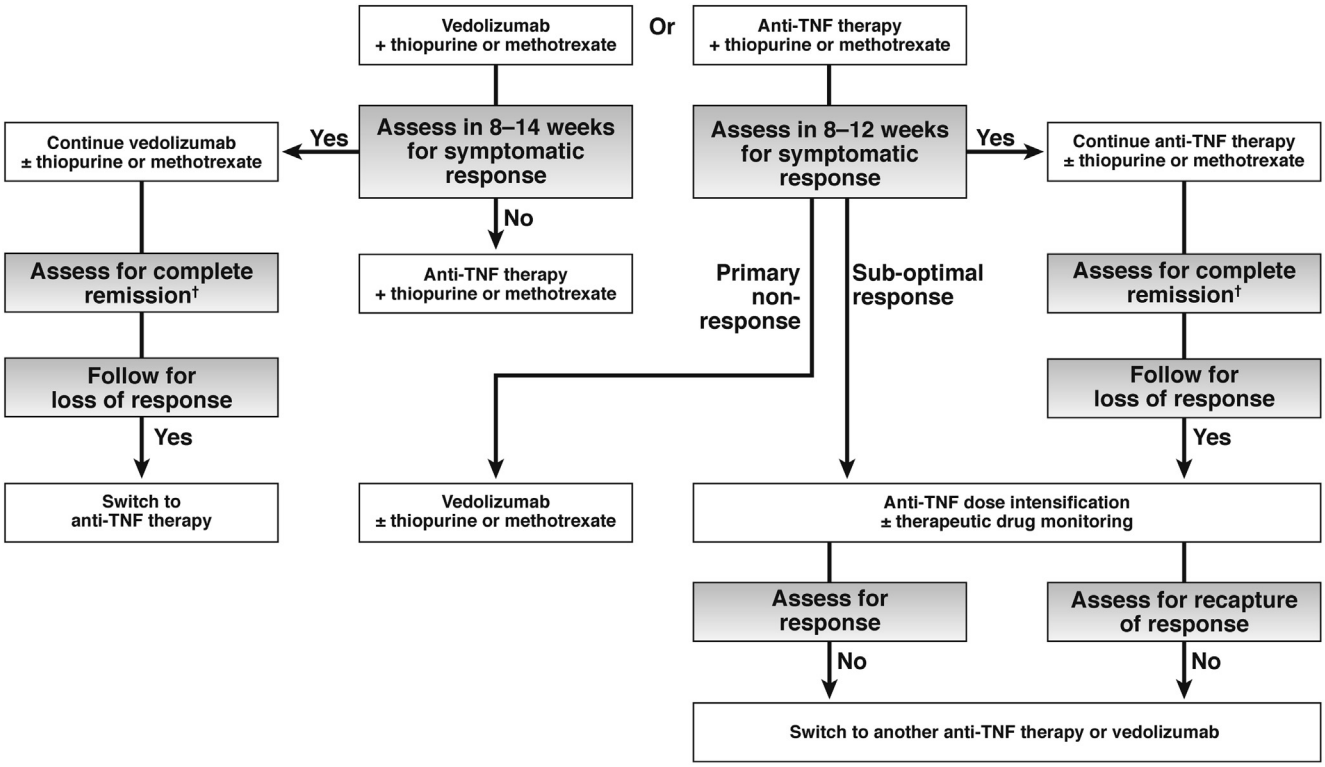

Figure 7. Consensus-guided algorithm for the management of corticosteroid-resistant/dependent UC[a]. [a]5-ASA is not appropriate for corticosteroid-resistant/dependent UC. †The optimal time to assess for complete remission is uncertain but is between 4 and 12 months after initiation of therapy. When complete remission is achieved, therapy should be continued.

A meta-analysis of 3 RCTs found that VSL#3, when added to conventional therapy, resulted in higher remission rates than conventional therapy alone (43.8% vs 24.8%; OR, 2.4; 95% CI, 1.48–3.88; $P = .0001$).[154] The quality of the individual studies used in these meta-analyses was insufficient to warrant a recommendation supporting the use of these agents. No significantly different adverse events were detected between probiotics and controls.[153] The negative results of the meta-analysis[153] for *Escherichia coli* Nissle were confirmed in another recent RCT, which found lower rates of clinical remission with adjunctive *E coli* Nissle compared with placebo.[155]

Similarly, there are currently insufficient data to support the routine use of nicotine,[156] tacrolimus,[157] cyclosporine,[158,159] phosphatidylcholine,[160–162] *Trichuris suis*,[163] or tofacitinib[164] in an ambulatory population. Studies on these agents are generally small and characterized by heterogeneity, indirectness, and imprecision, and the quality of evidence was assessed as very low. Cyclosporine has not been adequately studied outside the setting of acute severe UC.

Summary

Previous Canadian recommendations have addressed severe UC in the hospitalized patient,[9] and these guidelines present recommendations for the nonhospitalized patient with mild to severe active UC.

Consensus was reached on 34 statements pertaining to 5 main treatment options: 5-ASA, corticosteroids, immunosuppressants, anti-TNF therapies, and other therapies (Table 4). An algorithm summarizing the consensus-guided approach to the medical management of mild to severe active UC is shown in Figures 5 to 7. The goal of therapy is complete remission, including both symptomatic and endoscopic remission, with timely assessments of response and remission being a key factor in achieving this goal. Therapy should be continued, generally with the same agents used for induction (with the exception of corticosteroids), to maintain complete remission.

These guidelines should help to optimize the use and proper positioning of existing medical therapies and thus improve outcomes in patients with UC. However, unanswered questions remain. Further data are necessary to confirm the efficacy, safety, and optimal duration of combinations of therapy with TNF antagonists and immunosuppressive agents. In addition, there remain important questions related to prognostic biomarkers, risk stratification, individualized treatment algorithms, therapeutic drug monitoring, and alternatives to endoscopy for assessing disease control. The promise of new therapies, such as novel antagonists of leukocyte trafficking and JAK inhibitors,[165] may provide a broader range of therapies for patients with UC and will be considered in future iterations of these guidelines.

Appendix 1

Toronto Ulcerative Colitis Consensus Group

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.03.001.

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Speaker's Bureau: Abbott/AbbVie (AB, BF, CW, EJB, GVA, HS, JJ, JM, LPB, RPa, RPe, RS, SD, WA, WR), Alpco (BB), Amgen (RPa), Aptalis (AB, GVA, HS, JM, RPa, RS), Astra Zeneca (PT, RPa), Baxter (RPa), BMS (RPa), Centocor (RPa), Eisai (RPa), Elan/Biogen (RPa), Ferring (BB, GVA, HS, JM, LPB, RPa, WR), Forest (JM), GSK (RPa), HAC-pharma (LPB), Janssen (AB, BF, CS, CW, EJB, GN, GVA, HS, JJ, JM, LPB, MB, RPa, RS, SD, WA, WR), Johnson & Johnson (RPe), Merck (LPB, RPa), Millennium (RPa), MSD (WR), Novo Nordisk (BF), Norgine (LPB), Pendopharm (BB, MB), Pfizer (LT, PT, RPa), Pharmacosmos (WR), Proctor & Gamble (RPa), Prometheus (RPa), Schering-Plough (RPa), Shire (AB, BB, HS, JJ, JM, RPa, SD, WA), Takeda (BF, CW, HS, JJ, JM, LT, RPa, SD), Therakos (LPB), Tillotts (LPB), UCB Pharma (BF, RPa), Vifor (LPB), Warner Chilcott (AB, BB, BF, CS, GVA, JM, RPa, WA).

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For a list of voting participants in the Toronto Ulcerative Colitis Consensus Group, see Appendix 1.

Supplementary Appendix 1. Search Strategies Used for EMBASE, MEDLINE, and CENTRAL

EMBASE	MEDLINE	CENTRAL
1. ulcerative colitis/	1. Colitis, Ulcerative/	1. Colitis, Ulcerative/
2. (ulcer* adj2 colitis).tw.	2. (ulcer* adj2 colitis).tw.	2. (ulcer* adj2 colitis).tw.
3. (ulcer* adj2 proctitis).tw.	3. (ulcer* adj2 proctitis).tw.	3. (ulcer* adj2 proctitis).tw.
4. or/1-3	4. or/1-3	4. or/1-3
5. 5-Aminosalicylate*.tw.	5. 5-Aminosalicylate*.tw.	5. 5-Aminosalicylate*.tw.
6. 5-ASA.tw.	6. 5-ASA.tw.	6. 5-ASA.tw.
7. 5-aminosalicylic acid.tw.	7. 5-aminosalicylic acid.tw.	7. 5-aminosalicylic acid.tw.
8. mesalazine/	8. Mesalamine/	8. Mesalamine/
9. (Mesalamine or mesalazine).tw.	9. (Mesalamine or mesalazine).tw.	9. (Mesalamine or mesalazine).tw.
10. salazosulfapyridine/	10. Sulfasalazine/	10. Sulfasalazine/
11. (Sulfasalazine or salazosulfapyridine).tw.	11. (Sulfasalazine or salazosulfapyridine).tw.	11. (Sulfasalazine or salazosulfapyridine).tw.
12. balsalazide/	12. balsalazide.tw.	12. balsalazide.tw.
13. balsalazide.tw.	13. olsalazine.tw.	13. olsalazine.tw.
14. olsalazine/	14. Adrenal Cortex Hormones/	14. Adrenal Cortex Hormones/
15. olsalazine.tw.	15. (Corticosteroid* or steroid*).tw.	15. (Corticosteroid* or steroid*).tw.
16. corticosteroid/	16. Prednisone/	16. Prednisone/
17. (Corticosteroid* or steroid*).tw.	17. Prednisone.tw.	17. Prednisone.tw.
18. prednisone/	18. Hydrocortisone/	18. Hydrocortisone/
19. Prednisone.tw.	19. hydrocortisone.tw.	19. hydrocortisone.tw.
20. hydrocortisone/	20. (Methylprednisone or meprednisone).tw.	20. (Methylprednisone or meprednisone).tw.
21. hydrocortisone.tw.	21. Budesonide/	21. Budesonide/
22. prednisolone/	22. Budesonide.tw.	22. Budesonide.tw.
23. prednisolone.tw.	23. Glucocorticoids/	23. Glucocorticoids/
24. meprednisone/	24. Glucocorticoid*.tw.	24. Glucocorticoid*.tw.
25. (Methylprednisone or meprednisone).tw.	25. Thiopurine*.tw.	25. Thiopurine*.tw.
26. Budesonide/	26. 6-Mercaptopurine/	26. 6-Mercaptopurine/
27. Budesonide.tw.	27. mercaptopurine.tw.	27. mercaptopurine.tw.
28. glucocorticoid/	28. Azathioprine/	28. Azathioprine/
29. glucocorticoid*.tw.	29. Azathioprine.tw.	29. Azathioprine.tw.
30. Thiopurine*.tw.	30. Methotrexate/	30. Methotrexate/
31. mercaptopurine/	31. methotrexate.tw.	31. methotrexate.tw.
32. mercaptopurine.tw.	32. (tumor necrosis factor* adj1 antibod*).tw.	32. (tumor necrosis factor* adj1 antibod*).tw.
33. azathioprine/	33. Anti-tumor necrosis factor*.tw.	33. Anti-tumor necrosis factor*.tw.
34. Azathioprine.tw.	34. Anti-TNF.tw.	34. Anti-TNF.tw.
35. methotrexate/	35. infliximab.tw.	35. infliximab.tw.
36. methotrexate.tw.	36. (avakine or remicade or revellex).tw.	36. (avakine or remicade or revellex).tw.
37. tumor necrosis factor antibody/	37. etanercept.tw.	37. etanercept.tw.
38. Anti-tumor necrosis factor*.tw.	38. (Adalimumab or humira or trudexa).tw.	38. (Adalimumab or humira or trudexa).tw.
39. Anti-TNF.tw.	39. monoclonal antibody D2E7.tw.	39. monoclonal antibody D2E7.tw.
40. infliximab/	40. (Certolizumab or Cimzia).tw.	40. (Certolizumab or Cimzia).tw.
41. infliximab.tw.	41. (Natalizumab or Tysabri or Antegren).tw.	41. (Natalizumab or Tysabri or Antegren).tw.
42. (avakine or remicade or revellex).tw.	42. an100226.tw.	42. an100226.tw.
43. etanercept/	43. (Golimumab or cnto148 or simponi).tw.	43. (Golimumab or cnto148 or simponi).tw.
44. etanercept.tw.	44. (vedolizumab or MLN-02 or LDP-02 or MLN0002 or MLN-0002 or “MLN 0002” or LDP0002 or LDP-0002 or “LDP 0002” or UNII-9RV78Q2002).tw.	44. (vedolizumab or MLN-02 or LDP-02 or MLN0002 or MLN-0002 or “MLN 0002” or LDP0002 or LDP-0002 or “LDP 0002” or UNII-9RV78Q2002).tw.
45. adalimumab/	45. alpha4beta7 antibod*.tw.	45. alpha4beta7 antibod*.tw.
46. (Adalimumab or humira or trudexa).tw.	46. ((anti-alpha4beta7 or anti alpha4beta7) adj antibod*).tw.	46. ((anti-alpha4beta7 or anti alpha4beta7) adj antibod*).tw.
47. monoclonal antibody D2E7.tw.	47. Probiotics/	47. Probiotics/
48. certolizumab pegol/	48. VSL3.tw.	48. VSL3.tw.
49. (Certolizumab or Cimzia).tw.	49. E coli Nissle.tw.	49. E coli Nissle.tw.
50. natalizumab/	50. Escherichia coli Nissle.tw.	50. Escherichia coli Nissle.tw.
51. (Natalizumab or Tysabri or Antegren).tw.	51. bacteriotherap*.tw.	51. bacteriotherap*.tw.
52. an100226.tw.		
53. golimumab/		
54. (Golimumab or cnto148 or simponi).tw.		
55. vedolizumab/		
56. (vedolizumab or MLN-02 or LDP-02 or MLN0002 or MLN-0002 or “MLN		

Supplementary Appendix 1. Continued

EMBASE	MEDLINE	CENTRAL
0002" or LDP0002 or LDP-0002 or "LDP 0002" or UNII-9RV78Q2002).tw. 57. alpha4beta7 antibod*.tw. 58. ((anti-alpha4beta7 or anti alpha4beta7) adj antibod*).tw. 59. probiotic agent/ 60. VSL3/ 61. VSL3.tw. 62. E coli Nissle.tw. 63. Escherichia coli Nissle.tw. 64. bacteriotherap*.tw. 65. feces microflora/ 66. or/5-65 67. random:.tw. or placebo:.mp. or double-blind:.tw. 68. 4 and 66 and 67 69. (animal$ not human$).sh,hw. 70. 68 not 69 71. meta-analys:.mp. or systematic review.tw,pt. 72. 4 and 66 and 71 73. 72 not 69 74. practice guideline/ 75. (practice adj2 guideline*).tw. 76. guideline:.mp. 77. consensus development.mp. 78. or/74-77 79. 4 and 66 and 78 80. 79 not 69 81. 70 or 73 or 80 82. limit 81 to english language 83. child/ or newborn/ or exp infant/ or toddler/ or preschool child/ or school child/ 84. adult/ or exp aged/ or middle aged/ 85. 83 not (83 and 84) 86. 82 not 85	52. or/5-51 53. 4 and 52 54. randomized controlled trial.pt. 55. controlled clinical trial.pt. 56. placebo.ab. 57. random*.ab. 58. or/54-57 59. exp animals/ not humans.sh. 60. 58 not 59 61. 53 and 60 62. meta analysis.mp,pt. or systematic review.tw,pt. 63. 53 and 62 64. 63 not 59 65. Practice Guideline/ 66. practice guideline*.tw. 67. guideline:.mp. 68. consensus development.mp. 69. or/65-68 70. 53 and 69 71. 70 not 59 72. 61 or 64 or 71 73. limit 72 to english language 74. child/ or child, preschool/ or infant/ or infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/ or Pediatrics/ or Neonatology/ 75. adult/ or aged/ or "aged, 80 and over"/ or frail elderly/ or middle aged/ or young adult/ 76. 74 not (74 and 75) 77. 73 not 76	52. or/5-51 53. 4 and 52 54. child/ or child, preschool/ or infant/ or infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/ or Pediatrics/ or Neonatology/ 55. adult/ or aged/ or "aged, 80 and over"/ or frail elderly/ or middle aged/ or young adult/ 56. 54 not (54 and 55) 57. 53 not 56

Supplementary Appendix 2. Measuring Disease Activity in UC: Mayo Score

Stool frequency[a]	0 = Normal number of stools for this patient
	1 = 1–2 stools more than normal
	2 = 3–4 stools more than normal
	3 = 5 or more stools more than normal
Rectal bleeding[b]	0 = No blood seen
	1 = Streaks of blood with stool less than half the time
	2 = Obvious blood with stool most of the time or more
	3 = Blood passed alone
Findings on flexible proctosigmoidoscopy	0 = Normal or inactive disease
	1 = Mild disease (erythema, decreased vascular pattern, mild friability)
	2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
	3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment[c]	0 = Normal (there are no symptoms of colitis, the patient feels well, and the flexible proctosigmoidoscopy score is 0) (stool frequency = 0; rectal bleeding = 0; patient's functional assessment = 0; flexible proctosigmoidoscopy findings = 0)
	1 = Mild disease (mild symptoms and proctoscopic findings that were mildly abnormal) (the subscores should be mostly 1: stool frequency = 0 or 1; rectal bleeding = 0 or 1; patient's functional assessment = 0 or 1; flexible proctosigmoidoscopy findings = 0 or 1)
	2 = Moderate disease (more serious abnormalities and proctosigmoidoscopic and symptom scores of 1 or 2) (the subscores should be mostly 2: stool frequency = 1 or 2; rectal bleeding = 1 or 2; patient's functional assessment = 1 or 2; flexible proctosigmoidoscopy findings = 1 or 2)
	3 = Severe disease (the proctosigmoidoscopic and symptom scores are 2 to 3 and the patient probably requires corticosteroid therapy and possibly hospitalization) (the subscores should be mostly 3: stool frequency = 2 or 3; rectal bleeding = 2 or 3; patient's functional assessment = 2 or 3; flexible proctosigmoidoscopy findings = 2 or 3)
Patient's functional assessment[d]	0 = Generally well
	1 = Fair
	2 = Poor
	3 = Terrible

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[a]Each patient served as his or her own control to establish the degree of abnormality of stool frequency.

[b]The daily bleeding score represented the most severe day of bleeding.

[c]The physician's global assessment acknowledged the 3 other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

[d]This variable is not included in the 12-point index calculation but is considered a measure of general sense of well-being when determining the physician's global assessment score.