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American Gastroenterological Association Technical Review on the Management of Moderate to Severe Ulcerative Colitis

Siddharth Singh, MD, MS[1,*], **Jessica R. Allegretti, MD, MPH**[2,*], **Shazia Mehmood Siddique, MD, MS**[3], **Jonathan P. Terdiman, MD, MD**[4]

[1]Division of Gastroenterology, University of California, San Diego, La Jolla, CA,

[2]Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA

[3]Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

[4]Division of Gastroenterology, University of California, San Francisco, CA

Abstract

A subset of patients with ulcerative colitis (UC) present with, or progress to, moderate to severe disease activity. These patients are at high-risk for colectomy, hospitalization, corticosteroid-dependence, and serious infections. The risk of life-threatening complications and emergency colectomy is particularly high among those patients hospitalized with acute severe ulcerative colitis (ASUC). Optimal management of outpatients or inpatients with moderate-severe UC often requires the use of immunomodulator and/or biologic therapies including thiopurines, methotrexate, cyclosporine, tacrolimus, tumor necrosis factor (TNF)-α antagonists, vedolizumab, tofacitnib or ustekinumab, either as monotherapy, or in combination (with immunomodulators), to mitigate these risks. Decisions about optimal drug therapy in moderate-severe UC are complex, with limited guidance on comparative efficacy and safety of different treatments, leading to considerable practice variability. Therefore, the American Gastroenterological Association prioritized development of clinical guidelines on this topic. To inform the clinical guidelines, this technical review was completed in accordance with the GRADE framework. Focused questions in adult outpatients with moderate-severe UC included: (1) overall and comparative efficacy of different medications for induction and maintenance of remission in patients with or without prior exposure to TNF-α antagonists, (2) comparative efficacy and safety of biologic monotherapy vs. combination therapy with immunomodulators, (3) comparative efficacy of top-down (upfront use of biologics and/or immunomodulator therapy) vs. step-up therapy (acceleration to biologic and/or immunomodulator therapy only after failure of 5-aminosalicylates), and (4) role of continuing vs. stopping 5-aminosalicylates in patients being treated with immunomodulator and/or biologic therapy for moderate-severe UC. Focused questions in adults hospitalized with ASUC included: (5) overall and comparative efficacy of pharmacological interventions for inpatients refractory to corticosteroids, in reducing risk of colectomy, (6) optimal dosing regimens for intravenous

Address for Correspondence: Chair, Clinical Guidelines Committee, American Gastroenterological Association, National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814., natarodian@gastro.org, Telephone: (301) 941-2618.

*Both authors contributed equally to the manuscript

corticosteroids and infliximab in these patients and (7) role of adjunctive antibiotics in the absence of confirmed infections.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that generally begins in young adulthood and lasts throughout life.[1] Although the incidence and prevalence of UC has stabilized in Western Europe and North America (affecting >0.2% of the population), its incidence continues to rise in newly industrialized countries.[2] Based on population-based cohort studies, the majority of patients with UC have a mild to moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity.[3] However, about 14–17% of patients may experience an aggressive course, and one in five may require hospitalization for such an acute severe exacerbation. The 5 and 10-year cumulative risk of colectomy is 10–15% and though rates of early colectomy have declined, long-term colectomy rates have remained stable over time; a subset of hospitalized patients with acute severe ulcerative colitis (ASUC) have short-term colectomy rates of 25–30%.[4]. Besides significantly impacting quality of life and work productivity due to symptoms, UC also is associated with an increased risk of colorectal cancer. Predictors of an aggressive UC disease course and colectomy are young age at diagnosis (age <40y), extensive disease, severe endoscopic activity (presence of large and/or deep ulcers), presence of extra-intestinal manifestations, early need for corticosteroids and elevated inflammatory markers.[5] Patients with moderate to severe disease activity, corticosteroid-dependence or those at high risk of colectomy benefit from treatment with a variety of immunosuppressive agents, including immunomodulators and/or biologic agents, such as tumor necrosis factor (TNF)-α antagonists. The number of pharmacologic agents available to treat moderate-severe UC has grown over the last 5 years and now includes an anti-integrin agent (vedolizumab), an oral janus kinase inhibitor (tofacitinib) and an interleukin 12/23 antagonists (ustekinumab). With the availability of multiple treatment options with differences in efficacy and safety profiles, there is considerable practice variability in the use of these drugs in the treatment of outpatients and inpatients with moderate-severe UC.[6, 7] Variations in practice may have unintended negative consequences in patient outcomes. Therefore, the American Gastroenterological Association (AGA) prioritized this topic for generation of clinical guidelines. This technical review and the accompanying guidelines may be read in conjunction with a similar AGA technical review and guidelines on the management of patients of mild-moderate UC for a complete understanding of the pharmacological treatment landscape in UC.[8, 9]

Objectives of the Review

This technical review focuses on drugs and treatment strategies for the management of adult (≥18 years) outpatients with moderate-severe UC, and adult inpatients with ASUC. Patients with moderate-severe UC are those with moderate to severe disease activity based on Truelove-Witts criteria or Mayo Clinic score, patients who are corticosteroid-dependent or corticosteroid-refractory, and/or patients with severe endoscopic disease activity (large and/or deep ulcers).[5, 10, 11] ASUC is defined in hospitalized patients by the Truelove-Witts criteria: ⩾6 per day bloody stools per day along with at least one marker of systemic toxicity

that includes a pulse rate >90 beats per minute, temperature > 37.8C, hemoglobin <10.5 g/dl and/or an erythrocyte sedimentation rate >30 mm/h. Patients with ASUC, particularly those with multiple markers of systemic toxicity, are at very high risk of in-hospital colectomy.[12]

This technical review addresses the following clinical questions:

- Overall and comparative efficacy and safety of pharmacological therapies including thiopurines, methotrexate, TNF-α antagonists (infliximab, adalimumab, golimumab), vedolizumab, tofacitinib and ustekinumab for the induction and maintenance of remission in adult outpatients with moderate-severe UC, in patients with or without prior exposure to TNF-α antagonists;
- Comparative efficacy and safety of biologic monotherapy vs. in combination with immunomodulator agents (thiopurines or methotrexate) for the induction and maintenance of remission in adult outpatients with moderate-severe UC;
- Comparison of top-down (upfront use of biologics and/or immunomodulator therapy) vs. step-up treatment strategy (acceleration to biologic and/or immunomodulator therapy only after failure of 5-aminosalicylates [5-ASA]) in adult outpatients with moderate-severe UC;
- Benefit of continuing vs. stopping 5-ASA therapy in adult outpatients with moderate-severe UC, who have advanced to biologic and/or immunomodulator therapy;
- Optimal dosing regimen of intravenous corticosteroids in adults hospitalized with ASUC;
- Role of adjunctive antibiotics in the absence of confirmed infection in adults hospitalized with ASUC;
- Overall and comparative efficacy of different drug therapies in reducing the risk of short-term colectomy in corticosteroid-refractory adults hospitalized with ASUC;
- Optimal dosing regimen for infliximab in reducing the risk of short-term colectomy in adults hospitalized with ASUC, refractory to corticosteroids.

This technical review does not address the role of therapeutic drug monitoring in management of biologic-treated patients with moderate-severe UC (see separate AGA guidelines),[13, 14]optimal treatment targets and monitoring strategies in patients with moderate-severe UC, impact of pharmacological interventions on the risk of colorectal neoplasia in patients with UC, or the operative management of patients with moderate-severe UC. The results of this technical review were used to inform the development of the accompanying clinical guidelines on the pharmacological management of patients with moderate-severe UC.

METHODS

Overview

This technical review and the accompanying guideline were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[15] The members of the technical review panel were selected by the AGA Clinical Guidelines Committee based on their clinical content and guideline development methodological expertise, and went through a thorough vetting process for potential conflicts of interest in accordance with the Institute of Medicine guidance. Through an iterative process, the participants developed focused clinical questions on the management of moderate-severe UC. After the focused questions were approved by the AGA Governing Board (on February 27, 2018), the technical review team identified relevant outcomes, systematically reviewed and summarized the evidence for each outcome across studies, and then rated the quality of the evidence across all outcomes for each clinical question.

While the guidelines were in advanced stages of development, two pivotal clinical trials (first head-to-head trial comparing vedolizumab vs. adalimumab [VARSITY]; registrations trials of ustekinumab for induction and maintenance of remission in patients with moderate-severe UC [UNITI] (published in September 2019) and a critical safety update on tofacitinib from the U.S. Food and Drug Administration (FDA) (released July 2019) were published.[16–18] The technical review team and the guideline panel reviewed these important updates with the Clinical Guidelines Committee, which recommended a focused updated of the technical review and guidelines incorporating evidence from these studies.

Formulation of Clinical Questions and Outcome Measurement

Using the PICO format, which frames a clinical question by defining a specific Population (P), Intervention (I), Comparator (C), and Outcomes (O), the team finalized 12 questions to be addressed (Table 1). In outpatients with moderate-severe UC, induction and maintenance of clinical remission were considered critical outcomes for decision-making, whereas achieving endoscopic remission, corticosteroid-free remission, serious adverse events and treatment tolerability (drug discontinuation due to adverse events) were considered important outcomes. While risk of colectomy was also considered a critical outcome, clinical trials were not powered to measure this outcome, so inducing and maintaining clinical remission, outcomes strongly associated with decreasing risk of colectomy, was used a strong surrogate for avoidance of colectomy. Clinical remission was most commonly measured using the Mayo Clinic score (MCS), an index with scores ranging from 0–12, based on measures of stool frequency, rectal bleeding, physician global assessment, along with endoscopic disease activity.[11] Scores of 6–12 correspond to moderate to severe disease activity, whereas clinical remission is most consistently defined as MCS<3, with no individual sub-score >1. By current convention, endoscopic remission is defined as a sub-score of 0 or 1, implying that all patients in clinical remission by MCS would be in endoscopic remission too. In older trials, alternative cut-offs of MCS-defined remission and alternative disease activity indices such as Powell-Tuck index, Baron endoscopy score, and others were used. In these trials, if clinical and endoscopic outcomes were reported

separately, then data on clinical remission was used for analysis. If clinical remission was not reported, then clinical response was abstracted as a surrogate outcome.

In hospitalized patients with ASUC, risk of short-term colectomy (either in-hospital, or within 3 months) was considered as the critical outcome, whereas achieving clinical and endoscopic remission and serious adverse events were considered important outcomes. Long-term risk of colectomy, while deemed important could not adequately addressed through the short-term trials of interventions in patients with ASUC.

Estimating Absolute Magnitude of Benefit

In order to provide a synthesis of the risks and benefits of different interventions, to calculate absolute effect estimates, the technical review team relied on pooled placebo clinical remission rates. In trials of induction therapy with biologic agents and tofacitinib, induction of clinical remission with placebo was set at 10% (pooled rate, 8.9%), and maintenance of clinical remission was set at 15% (pooled rate, 13.1%).[19] In trials of thiopurines which reported steroid-free remission as outcome, pooled rates across placebo arms were used. Similarly, in trials in patients with ASUC, pooled rates short-term colectomy in corresponding placebo arms were used.

Search Strategy and Study Selection Criteria

An experienced medical librarian performed a systematic literature search of multiple electronic databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, and Wiley Cochrane Library) using a combination of controlled vocabulary terms supplemented with keywords. The search was conducted on March 18, 2018. For evidence synthesis, randomized controlled trials (RCTs) conducted in adults with moderate-severe UC and in patients hospitalized with ASUC evaluating interventions of interest (corresponding to relevant PICOs) were included. If RCT-level evidence was not available for specific PICOs, then observational studies were included to inform evidence. Minimum trial duration for induction and maintenance therapy was 2 weeks and 16 weeks, respectively. Trials in patients with Crohn's disease were excluded; if a trial included both patients with UC and Crohn's disease, it was included only if results were stratified by disease or if >70% participants had UC. Since safety outcomes are not well informed by RCTs, representative large cohort studies and high-quality systematic reviews/meta-analyses were used to inform risk of serious infections and malignancy with different therapies. Separate systematic literature reviews were performed to identify studies informing cost-effectiveness and patients' values and preferences for different management strategies in moderate-severe UC. In addition, studies on issues of racial, ethnic, and social disparities and issues of general health equity pertinent to the topic were identified. Details of the search strategy are reported in the Online Supplement. Total 11,947 articles were identified.

Subsequently, a focused literature search for evidence on biologics or tofacitinib in outpatients with moderate-severe UC was performed on October 1, 2019, when the Clinical Guidelines Committee recommended updating the review.

Data Extraction and Statistical Analysis

Data abstraction was conducted in duplicate, independently, by two investigators (SS and SMS), with disagreements or questions of accuracy resolved by discussion and consensus with the technical review team.

For trials of induction and maintenance therapy, outcomes were abstracted and reported as failure to induce clinical remission (in patients with active disease), and failure to maintain remission (in patients with quiescent disease at trial entry), respectively. All analyses were conducted using true intention-to-treat analysis; patients lost to follow-up or excluded from analysis for other reasons were deemed to be treatment failures. Pooled relative risk (RR) or odds ratios (OR) and 95% confidence intervals (CI), were calculated using the Mantel-Haenszel fixed-effects model (in the absence of conceptual heterogeneity and if <5 studies) or the DerSimonian-Liard random-effects model.[20] Statistical heterogeneity was assessed using the I^2 statistic.[21] Small study effects were examined using funnel plot symmetry and Egger's regression test, though it is important to recognize that these tests are unreliable when the number of studies is <10.[22] Direct comparisons were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark). Due to a paucity of head-to-head trials of active agents, to inform comparative efficacy of different pharmacologic interventions, we performed network meta-analysis using a multivariate, consistency model, random-effects meta-regression as described by Ian White, using STATA v.13.0 (College Station, TX).[23, 24] This approach provides a point estimate from the network along with 95% CI from the frequency distribution of the estimate. This approach of using network meta-analysis has previously been used in AGA guidelines and other societies.[25–28]

Quality of Evidence

The quality of evidence was judged using the GRADE framework. For questions of comparative efficacy of different pharmacological interventions for which effect estimates were derived from the direct and the network meta-analysis, we used the following approach: when direct evidence was available from head-to-head comparisons, this was considered the best available evidence; if there were no direct comparisons between two interventions (and hence, no direct meta-analysis was feasible), effect estimates from the network meta-analysis were used. In applying GRADE to network meta-analysis, first we judged the quality of evidence for direct comparisons then we rated the indirect estimates, starting at the lowest rating of the two pairwise estimates that contributed as first-order loops.[29] We rated down further for imprecision or intransitivity (i.e. dissimilarity between studies in terms of clinical or methodological characteristics). It is important to note that GRADE in the context of clinical guidelines may be different than GRADE in the context of systematic reviews, since the former relies on more comprehensive assessment of risks and benefits, with varying thresholds of confidence for decision-making.

Evidence-to-Decision Framework

Since this technical review was used to inform the development of clinical guidelines, besides a comprehensive risk-benefit analysis, information about additional factors such as patients' values and preferences, cost-effectiveness, and resource utilization were also reviewed.[30] These data are summarized in the Results section.

RESULTS

Safety of Pharmacological Therapies for Moderate-Severe UC

Before discussing the focused questions related to the efficacy and comparative efficacy of pharmacologic therapies for moderate-severe UC and ASUC, we have briefly summarized the overall and comparative safety of different pharmacological interventions in large cohort studies and clinical trials, focusing on serious infections and malignancy. It is important to note that clinical trials are selective in enrollment, and often have short follow-up, and data from these trials are often not able to adequately assess the safety of different therapies.

Risk of Serious and Opportunistic Infections: Findings from key nationwide or nationally representative cohort studies on risk of serious and opportunistic infections with IBD pharmacotherapies have been summarized in eTable 1.[31–35] Across studies, most consistent risk factors for serious infections are high disease activity and inadequate disease control, need for corticosteroids and opiate medication and concomitant use of immunomodulators.[36–40]

Immunomodulators and/or TNF-α antagonists: Overall risk of serious infections (infections requiring hospitalizations) in patients treated with immunomodulator monotherapy, TNF-α antagonist monotherapy or combination therapy was generally <1%. Risks are higher in older patients, with multi-morbidity. On comparative evaluation, some studies demonstrate that risk of serious infections may be 1.1–2.0 times higher with TNF-α antagonist monotherapy vs. immunomodulator monotherapy. In a population-based French cohort, Kirchgesner and colleagues observed that monotherapy with immunomodulators or TNF-α antagonists was associated with <0.2% risk of opportunistic infections, and combination therapy may be associated with ~2-times higher risk of opportunistic infections as compared to monotherapy with either agent.[31] In a retrospective cohort study using Medicare-Medicaid databases, Lewis and colleagues observed that the risk of serious infections with TNF-α antagonists was not significantly different than risks with prolonged corticosteroids, and the former was associated with lower mortality.[34]

Vedolizumab: Long-term safety data on vedolizumab in patients with IBD are lacking. Since vedolizumab selectively blocks gut-specific lymphocyte trafficking, it is presumed to have superior safety profile as compared to other biologics and small molecules, but this remains unproved. Integrated safety analysis from registration trials of vedolizumab (2830 patients with 4811 person-years of follow-up) showed that the risk of serious infections was low, and not significantly different than rates in placebo-treated patients.[36] Among patients with UC, the incidence rate of serious infections was 2.7 per 100 p-y, with upper respiratory infections being the most common. The rate of gastrointestinal infections was numerically higher in vedolizumab-treated patients, than placebo-treated patients. Six post-marketing cohort studies with short follow-up demonstrated that the rate of infection was 8%, including 2% rate of enteric infections.[41] To date, one case of progressive multifocal leukoencephalopathy has been reported in a vedolizumab-treated patient who was also diagnosed with acquired immunodeficiency syndrome and the disease was felt to be unrelated to vedolizumab.

Tofacitinib: With its recent regulatory approval for UC, long-term safety data for tofacitinib in UC are lacking. In an integrated safety analysis of 1157 tofacitinib-treated patients (1613 person-year follow-up) in phase II/III and open-label long-term extension studies of tofacitinib in UC, the incidence rate of serious and opportunistic infections was 2.0 and 1.3 per 100 person-years.[42] Specifically, the annual incidence rate of herpes zoster was 4.1 (95% CI, 3.1–5.2) per 100 person-years, with higher risk being observed in older patients, Asian patients, patients with prior TNF-α antagonist exposure and in patients receiving 10mg BID dose. Overall, 11/65 patients had multi-dermatomal involvement, and 1 developed encephalitis; 5/65 (7.7%) events led to treatment discontinuation.[43]

In July 2019, the FDA released a key safety warning regarding tofacitinib 10mg twice/day, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis.[18] In 2012, when FDA first approved tofacitinib for rheumatoid arthritis, FDA required a post-marketing clinical trial (comparing tofacitinib 5mg twice/day vs. tofacitinib 10mg twice/day vs. TNFα antagonists) in patients with rheumatoid arthritis on background methotrexate, to evaluate the risk of cardiac events, cancer, and infections. In the interim safety analysis of this trial till January 2019, an excessive rate of pulmonary embolism and all-cause mortality was identified in patients treated with tofacitinib 10mg twice/day as compared to patients treated with TNFα antagonists. Overall, incidence rate of pulmonary embolism and all-cause mortality in patients treated with tofacitinib 10mg twice/day was 0.49 per 100py (19 cases in 3884py) and 1.15 per 100py (45 deaths in 3884py), respectively, and corresponding rates in TNFα antagonist-treated patients with rheumatoid arthritis was 0.075 per 100py (3 cases in 3982py) and 0.63 per 100py (25 deaths in 3982py), respectively. Based on these findings, the FDA modified the labeling for tofacitinib across all indications. In select cases, tofacitinib 10mg twice/day dosing may be considered for >8 weeks such as in cases of loss of response but should only be used for the shortest duration and only after careful consideration of the risks and benefits of the drug. Tofacitinib should also be used cautiously in patients with an increased risk of thrombosis, the drug should be discontinued in patients with signs or symptoms of a thrombosis.

Ustekinumab: With its recent regulatory approval for UC, long-term safety data for ustekinumab in UC are lacking. In an integrated safety analysis of data from 6 phase 2/3 trials of ustekinumab including 2574 patients (1733py), incidence of serious infections was 5.02 per 100py (vs. 5.53 in placebo-treated patients).[44] Extrapolating from other autoimmune diseases like psoriasis, the risk of serious infections with ustekinumab monotherapy may be lower as compared to TNFα antagonist monotherapy. In the BADBIR registry (British Association of Dermatologists Biologic Interventions Register) of biologic therapies in psoriasis, the incidence rate of serious infections with ustekinumab was 1.5 per 100py, and the risk was not higher compared with other non-biologic systemic therapies (HR, 0.92 [0.60–1.41]).[45] In the US PSOLAR (Psoriasis Longitudinal Assessment and Registry) registry with 12,093 patients (40,388py follow-up), absolute risk of serious infections with ustekinumab (0.93 per 100py) was lower as compared to infliximab (2.91 per 100py) and other biologic agents (1.91 per 100py).[46] These findings on the relative safety of ustekinumab in patients with psoriasis should be interpreted with caution, though, since the

dose of ustekinumab approved for use in UC is at least 50% higher than the dose used in psoriasis.

Risk of Malignancy: Findings from key nationwide or nationally representative cohort studies on risk of malignancy with IBD pharmacotherapies have been summarized in eTable 2.[47–51]

Thiopurines: Thiopurines have been consistently associated with increased risk of lymphoproliferative diseases. In a meta-analysis of 18 studies, the standardized incidence rate of lymphoma in thiopurine-treated patients was 4.9 (95% CI, 3.1–7.8), with higher rates being reported in referral-center studies (SIR, 9.2) vs. population-based studies (SIR, 2.8).[52] The level of risk was statistically significant after 1 year of exposure, and risk was elevated in current (SIR, 5.7), but not former users (SIR, 1.4). On modeling, Kotlyar and colleagues estimate the number of patients needed to be treated with thiopurines to cause 1 additional lymphoma ranges from 4598 in those 20–29 years to 325 in those 70–79 years. In another meta-analysis of 8 studies, Ariyaratnam and Subramanian estimated a 2.3-times higher risk of non-melanoma skin cancer in thiopurine-treated patients (95% CI, 1.5–3.5).[53] Methotrexate has been variably associated with either no significant or a 1.5–5.0-times increased risk of lymphoproliferative disease, based on studies in patients with rheumatoid arthritis.[54–56]

TNF-α antagonists: Several large population-based studies have identified no association between TNF-α antagonist exposure and solid-organ malignancy. TNF-α antagonists have been variably associated with a 2–5-fold increased risk of lymphoid malignancy in population-based studies. In a French population-based study, Lemaitre and colleagues estimated the annual incidence of lymphoma in patients treated with TNF-α antagonist monotherapy vs. unexposed patients to be 0.41 per 1000 person-years vs. 0.26 per 1000 person-years; after adjusting for covariates, risk of lymphoma was 2.4-times higher in patients treated with TNF-α antagonist monotherapy.[47] This risk was comparable to risk observed in patients treated with thiopurine monotherapy (OR, 0.93; 95% CI, 0.60–1.44). Patients exposed to combination therapy had 6.1-times higher of lymphoma, as compared to unexposed patients, and 2.3–2.5 times higher risk as compared to patients exposed to monotherapy with either agent. In contrast, long-term follow-up of clinical trials or registry-based studies have not observed an increased risk of malignancy in patients treated with TNF-α antagonist monotherapy.[57–59] On analysis of 1594 patients with Crohn's disease treated with adalimumab in clinical trials, over 3050 person-years of exposure, Osterman and colleagues observed an increased risk of malignancy with in patients treated with combination therapy (SIR, 3.0; 95% CI, 1.7–5.1), but not adalimumab monotherapy (SIR, 0.6; 95% CI, 0.2–1.6).[58] Compared with patients receiving adalimumab monotherapy, those patients receiving combination therapy had an increased risk of malignancy other than non-melanoma skin cancer (RR, 2.8; 95% CI, 1.1–7.4) and of non-melanoma skin cancer (RR, 3.5; 95% CI, 1.1–11.1). In a large prospective registry (PYRAMID) of 5025 adalimumab-treated patients with Crohn's disease over 16680.4 person-years of follow-up, observed lymphoma rate with adalimumab was lower than the estimated background rate.[59] Regardless, the FDA has issued a black box warning on the increased risk of malignancy

with TNF-α antagonists (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf, accessed August 21, 2018).

Vedolizumab: Although long-term follow-up and real-world evidence is lacking, safety analyses of clinical trials and open-label extension studies have not observed any significant increase in risk of solid-organ or hematological malignancies with vedolizumab. Colombel and colleagues reported malignancy in 18/2830 patients with vedolizumab exposure vs. 1/504 placebo-treated patients; 6/18 were gastrointestinal cancers.[36] Indirect treatment comparison network meta-analysis of 23 RCTs suggested no difference in risk of malignancy between patients treated with TNF-α antagonist vs. vedolizumab (OR, 0.87; 95% CI, 0.26–2.88).[60]

Tofacitinib: While long-term safety studies are lacking, analysis of clinical trials and open-label extension studies of tofacitinib in UC to date, suggests an annual incidence rate of malignancy excluding non-melanoma skin cancer of 0.5 per 100 person-years.[42]

Ustekinumab: In an integrated safety analyses of phase II/III trials of ustekinumab for psoriasis, psoriatic arthritis and CD, the incidence of malignancy (excluding NMSC) was low and comparable among ustekinumab-treated patients (0.4 per 100py) and placebo-treated patients (0.2 per 100py).[44] Combined across indications, the standardized incidence rate for malignancies (excluding cervical cancer in situ and NMSC per SEER) in the ustekinumab and placebo groups were 0.6 (0.3–1.0) and 0.3 (0.0–1.9), respectively, with overlapping 95% CIs.

Other side effects associated with these medications are summarized in the online supplement.

Pharmacological management of patients with moderate to severe ulcerative colitis

Question 1.—In adult outpatients with moderate-severe UC, what is the efficacy of the TNF-α antagonists (infliximab, adalimumab, golimumab), vedolizumab, tofacitinib and ustekinumab for induction and maintenance of remission?

Key Message: Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib and ustekinumab are more effective than placebo for induction and maintenance of remission in adult outpatients with moderate-severe UC (*moderate to high quality evidence*)

Effect estimate: Overall, 16 RCTs informed the efficacy of different biologic drugs, and tofacitinib, in patients with moderate-severe UC (eTable 3). Patients across all trials and treatment arms were comparable in terms of baseline prognostic variables, inclusion/exclusion criteria, and co-interventions. All outcomes were uniformly assessed based on standard definition of Mayo Clinic Score, between weeks 6 to 8 for induction therapy and week 30 to 54 for maintenance therapy. Relative and absolute effect estimates are shown in Table 2.

Infliximab vs. placebo: All trials evaluating the efficacy of infliximab were conducted in biologic-naïve patients. Based on five RCTs (710 patients), standard infliximab induction

therapy (5mg/kg intravenously at weeks 0, 2, 6) was superior to placebo for induction of remission (RR, 2.85; 95% CI, 2.11–3.86).[61–64] Four treat-straight-through trials of maintenance therapy of infliximab were identified in which patients with active UC were randomized to infliximab vs. placebo and followed for 26–54 weeks. In these trials, infliximab was superior to placebo for maintenance of remission.

Adalimumab vs. placebo: Based on three trials (940 patients), standard induction therapy with adalimumab was superior to placebo for induction of remission.[65–67] Of note, two trials were conducted in biologic-naïve patients, whereas in one trial (ULTRA 2), ~40% had prior exposure to a TNF-α antagonist, with either intolerance or secondary loss of response, however, none of these patients had prior primary non-response to a TNF-α antagonist. In a subset of patients with prior exposure a TNF-α antagonist, adalimumab was not significantly superior to placebo for induction of remission (RR, 1.36; 95% CI, 0.49–3.80), though the trial was not powered to address this subpopulation. Based on two treat-straight-through trials, adalimumab was superior to placebo for maintenance of remission.

Golimumab vs. placebo: Based on two trials of induction therapy (644 patients) conducted in biologic-naïve patients, golimumab was superior to placebo for induction of clinical remission in patients with moderate-severe UC.[68, 69] In contrast to trials of maintenance therapy with infliximab or adalimumab, trials of maintenance therapy with golimumab included only patients with clinical response to induction therapy with golimumab. In these patients, golimumab was superior to placebo for maintenance of clinical remission.

Vedolizumab vs. placebo: Based on two trials (624 patients), vedolizumab was superior to placebo for induction of clinical remission in patients with moderate-severe UC.[70, 71] In a subset of patients, who had prior exposure to a TNF-α antagonist, vedolizumab was not superior to placebo for induction of remission (RR, 1.66; 95% CI, 0.67–4.11). Among patients with clinical response to vedolizumab at week 6 or 10, two trials of maintenance therapy demonstrated that vedolizumab was superior to placebo for maintenance of remission.

Tofacitinib vs. placebo: Based on three trials (1220 patients), tofacitinib 10mg twice daily was superior to placebo for induction of clinical remission.[72, 73] These results were significant even in a subset of patients with prior TNF-α antagonist exposure (RR, 12.57; 95% CI, 2.46–64.12). Among patients re-randomized after clinical response to induction therapy, tofacitinib was superior to placebo for maintenance of remission (tofacitinib 5mg twice daily dosing vs. placebo: RR, 3.09; 95% CI, 1.99–4.79).

Ustekinumab vs. placebo: Based on one trial (641 patients), ustekinumab was superior to placebo for induction of clinical remission in patients with moderate-severe UC.[16] In a subset of patients, who had prior exposure to a TNF-α antagonist, ustekinumab was superior to placebo for induction of remission (RR, 10.18; 95% CI, 2.43–42.73). Among patients with clinical response to ustekinumab at week 8, one of maintenance therapy demonstrated that ustekinumab was superior to placebo for maintenance of remission.

GRADE Quality of Evidence: Table 2 summarizes the GRADE quality of evidence for the studies referenced above. Most of the studies of were conducted as registration trials, sponsored by industry. There was no important inconsistency or indirectness identified. The number of events was <200 for all comparisons, however, so the evidence was rated down for imprecision due to failure to reach optimal information size. In summary, there was moderate confidence in the estimates supporting all interventions vs. placebo for induction and maintenance of clinical remission.

Potential Harms of Intervention: Adverse effects associated with different medications have been summarized above. In addition, safety data from the pivotal clinical trials of maintenance therapies with these agents are summarized are summarized in eTable 4.

Discussion: Multiple well-designed registration trials of biologic drugs and tofacitinib have confirmed the superiority of these interventions over placebo for induction and maintenance of remission in patients with moderate-severe UC. All of these drugs have been approved by the FDA for this indication. Infliximab and adalimumab have also been shown to decrease the risk of hospitalization and colectomy in controlled studies in these patients. Comparable data on the impact of golimumab, vedolizumab, ustekinumab and tofacitinib on outcomes related to healthcare utilization are awaited. In another recent trial, VISIBLE 1, a new subcutaneous formulation of vedolizumab (108mg SQ every 2 weeks) was compared to conventional intravenous vedolizumab 300mg every 8 weeks in a subset of patients who responded to induction therapy with intravenous vedolizumab.[74] In this trial, there was no significant differences in rates of maintaining remission amongst those randomized to subcutaneous vs. intravenous vedolizumab. This subcutaneous forumation of vedolizumab is currently under FDA review, and would be an attractive alternative to intravenous vedolizumab for maintenance of remission, after induction therapy with the intravenous formulation.

Question 2.—In adult outpatients with moderate-severe UC, what is the comparative efficacy of the different biologic agents (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) and tofacitinib for induction and maintenance of clinical remission, in biologic-naïve patients, and in patients with prior TNF-α antagonist exposure?

Key Message #1: In biologic-naïve patients with moderate-severe UC, infliximab is probably superior to adalimumab (*moderate quality evidence*) and may be superior to golimumab, vedolizumab, tofacitinib and ustekinumab (*low to very low quality evidence*) for induction of remission.

Key Message #2: In biologic-naïve patients with moderate-severe UC, vedolizumab is probably superior to adalimumab for achieving remission (*moderate quality evidence*). The benefit of vedolizumab over golimumab, tofacitinib and ustekinumab for induction of remission is uncertain (*low to very low quality evidence*).

Key Message #3: In biologic-naïve patients with moderate-severe UC, the benefit of golimumab, tofacitinib, ustekinumab or adalimumab, over other comparator medications, for induction of remission is uncertain (*low to very low quality evidence*).

Key Message #4: In patients with moderate-severe UC with prior TNFα antagonist exposure, both ustekinumab and tofacitinib may be superior to adalimumab and vedolizumab for induction of remission (*low quality evidence*). The benefit of ustekinumab over tofacitinib, for induction of remission is uncertain (*very low quality evidence*).

Key Message #5: In patients with moderate-severe UC with prior TNFα antagonist exposure, the benefit of vedolizumab over adalimumab for achieving remission is uncertain (*very low quality evidence*). There is very limited evidence to inform the overall and comparative efficacy of infliximab and golimumab in patients with prior TNF-α antagonist exposure.

Key Message #6: In patients with moderate-severe UC who respond to induction therapy with the index agent, regardless of prior TNF-α antagonist exposure, the benefit of any biologic agent or tofacitinib over another for maintenance of remission is uncertain (*very low quality evidence*).

Effect Estimates and Quality of Evidence:

Induction of Remission, biologic-naïve patients: Only a single head-to-head trial was identified. In the VARSITY trial, patients with moderate-severe UC were randomized to standard doses of vedolizumab vs. adalimumab and treated through week 52.[17] At week 52, rate of clinical remission was significantly higher in vedolizumab-treated patients vs. adalimumab-treated patients (34.2% vs. 24.3%; RR, 1.41; 95% CI, 1.10–1.81) amongst biologic-naïve patients. Evidence from this head-to-head trial was considered to be of moderate quality (rated down for imprecision due to low event rate). For all other comparisons, evidence on comparative efficacy was derived from a network meta-analysis. Overall, 15 RCTs including 3747 biologic-naïve patients with moderate-severe UC, treated with infliximab (4 trials, 667 patients), adalimumab (4 trials, 1046 patients), golimumab (2 trials, 586 patients), vedolizumab (3 trials, 630 patients), tofacitinib (2 trials, 520 patients) and ustekinumab (1 trial, 298 patients) were included. Results of network meta-analysis, and pairwise meta-analysis are summarized in Table 3 and eFigure 1A. There was moderate confidence in estimates demonstrating the superiority of infliximab over adalimumab (OR, 2.10; 95% CI, 1.16–3.79) (evidence rated down for serious imprecision). Against all other agents though the effect estimates favored infliximab (OR, 1.46–2.00), all estimates were very imprecise and did not reach statistical significance. None of the other agents were clearly superior to any other agent for induction of remission. In comparing TNF-α antagonists, vedolizumab and ustekinumab vs. tofacitinib, in biologic-naïve patients, evidence was rated down due to intransitivity. This was due to difference in definition of outcome in trials of tofacitinib, which required rectal bleeding score to be 0 (instead of 0 or 1).

Induction of Remission in patients with prior TNFα antagonist exposure: Only a single head-to-head trial was identified. In the VARSITY trial, ~21% patients had received prior treatment with a TNFα antagonist other than adalimumab. In these patients, there was no significant differences in rates of achieving clinical remission at week 52 (20.3% vs. 16.0%), and the overall body of evidence was deemed to be low quality (rated down for very serious

imprecision). For all other comparisons, evidence of comparative efficacy was derived from a network meta-analysis. Overall, 7 RCTs including 1580 patients with moderate-severe UC with prior exposure to TNF-α antagonist were identified. There were no trials of infliximab or golimumab in patients with prior exposure to TNF-α antagonist, which met inclusion criteria. Results of network meta-analysis, and pairwise meta-analysis are summarized in Table 4 and eFigure 1B. There was low confidence in estimates supporting higher efficacy of tofacitinib and ustekinumab over adalimumab (tofacitinib vs. adalimumab: OR, 11.05; 95% CI, 1.79–68.41; ustekinumab vs. adalimumab: OR, 10.71; 95% CI, 2.01–57.20), and over vedolizumab (tofacitinib vs. vedolizumab: OR, 6.18; 95% CI, 1.00–38.00); ustekinumab vs. vedolizumab: OR, 5.99; 95% CI, 1.13–31.76) for induction of clinical remission in patients with prior exposure to TNFα antagonists. For all comparisons of different interventions in patients with prior TNF-α antagonist exposure, evidence was rated down for intransitivity. Prior treatment exposure and response is an important effect modifier. Study level estimates did not report what proportion of patients had exposure to more than one TNF-α antagonist and whether patients had exposure to multiple different classes of biologics.

Maintenance of Remission: Results of the VARSITY head-to-head trial have been reported earlier. A network meta-analysis of all interventions was deemed infeasible due to intrinsic differences in clinical trial design – trials of infliximab, adalimumab and VARSITY were treat-straight-through, whereas trials of golimumab, vedolizumab, tofacitinib and ustekinumab re-randomized only responders to induction therapy. Additionally, these trials did not consistently present data stratified by prior biologic exposure, leading to intransitivity (Table 5). Results of pairwise meta-analysis by trial design is shown in eFigures 2A and B. On indirectly comparing treat-straight-through maintenance trials of infliximab vs. adalimumab vs. vedolizumab, no differences were observed between interventions; similarly, on comparing maintenance trials of golimumab, vedolizumab, tofacitinib and ustekinimab, in which only responders to induction therapy were re-randomized, no meaningful differences were observed between the interventions. However, the overall quality of evidence was rated as very low quality evidence (rated down for very serious imprecision, intransitivity).

Potential Harms of Intervention: There has been very limited direct assessment of comparative safety of different biologic interventions or tofacitinib. In a published network meta-analysis of clinical trials of maintenance therapy (excluding ustekinumab), Singh and colleagues observed no significant difference in the risk of any serious adverse event between active interventions and placebo; instead, there was a trend towards lower risk of serious adverse events with vedolizumab vs. placebo (OR, 0.47; 95% CI, 0.21–1.06).[19] In the same analysis, rate of serious infections was low, and was not deemed amenable to network meta-analysis. Using risk of overall infections as a surrogate safety outcome, the investigators observed that golimumab (OR, 1.85; 95% CI, 1.20–2.86) and tofacitinib (OR, 1.75; 95% CI, 1.13–2.70) were associated with increased risk of infections as compared to placebo. There was numerically higher risk of infections with infliximab (OR, 1.30; 95% CI, 0.92–1.83) and adalimumab (OR, 1.23; 95% CI, 0.91–1.65), as compared to placebo, though this did not reach statistical significance. There was no significant increase in the risk of infections with vedolizumab (OR, 1.03; 95% CI, 0.60–1.79) as compared to placebo. In a

population-based cohort study in Denmark in biologic-naïve patients with UC comparing infliximab vs. adalimumab, a higher risk of serious infections requiring hospitalization was observed in adalimumab-treated patients as compared to infliximab-treated patients;[75] however, this has not been observed in other studies.[76] Real-world comparative safety data on vedolizumab, tofacitinib and ustekinumab (in patients with UC) are awaited.

Discussion: In the absence of head-to-head trials, evidence derived from indirect comparisons may be used to inform clinical practice and guidelines.[25–28] We performed a network meta-analysis to compare the efficacy of the drugs used to treat moderate-severe UC. All the trials included in the analysis, involved biologic-naïve patients, had comparable inclusion criteria, trial design, prevalence of risk factors that likely influence treatment response, and used similar outcome measures. Therefore, in the opinion of the technical review team, a comparison across trials could be undertaken without the introduction of significant intransitivity. Though all TNF-α antagonists have similar mechanism of action, the differences in efficacy between infliximab, adalimumab and golimumab may be related to difference in the pharmacokinetics and bioavailability of the drugs given their different dosing schema and route of administration. Limited real-world observational studies have also suggested a lower risk of hospitalization, corticosteroid use and serious infections in infliximab-treated patients as compared to adalimumab-treated patients. The recent SERENE-UC trial comparing standard- vs. high-dose adalimumab in patients with moderate-severe UC failed to demonstrate superiority of higher dose adalimumab, suggesting that currently approved dosing of adalimumab is unlikely to change.[77] Rate of induction of endoscopic remission was higher in infliximab- vs. golimumab-treated patients in the network meta-analysis. In an individual patient-level analysis of pivotal clinical trials of infliximab and golimumab in patients with moderate-severe UC, Singh and colleagues observed that infliximab was associated with more rapid resolution of symptoms, and greater efficacy for inducing remission than golimumab, after adjusting for important covariates.[78] Ongoing head-to-head trials would further enhance clinical decision-making and our confidence in comparative efficacy of different medications.

In contrast to biologic-naïve patients, the technical review team was concerned about significant intransitivity in trials comparing patients with prior TNF-α antagonist exposure. Patients treated with adalimumab or golimumab in clinical trials generally had exposure to only a single TNF-α antagonist. In contrast, in trials of vedolizumab, or tofacitinib, a significant proportion of patients may have been exposed to 2 or more biologic agents prior to clinical trial intervention and may be inherently be difficult to treat; in trials of ustekinumab, ~15% had been previously exposed to vedolizumab also, besides exposure to TNF-α antagonist(s). Similarly, there may be potential differences in efficacy of 2nd line interventions depending on underlying reason for discontinuation of prior TNF-α antagonist (primary non-response vs. secondary loss of response vs. intolerance).[79] In trials of adalimumab, only patients with loss of response or intolerance to a prior TNF-α antagonist were included; patients with primary non-response to TNF-α antagonist were excluded. In contrast, in trials of vedolizumab, 48% patients had inadequate response to TNF-α antagonist (primary non-response). Because of these important uncertainties and differences between study populations, we opted to rate down evidence for intransitivity the evidence

regarding prior TNF-α antagonist exposed patients. The mechanistic reason behind the apparent superior efficacy of ustekinumab and tofacitinib over vedolizumab and adalimumab amongst patients with prior TNFα antagonists is unclear, and needs to be verified in prospective trials.

Trials of maintenance therapy had different design, which limited reasonable indirect comparability. Hence, most of the evidence derived was deemed very low quality.

Safety is a key factor in clinical decision-making. However, there was limited evidence to inform comparative safety of different interventions. Besides the intrinsic safety profile of individual medications, the most consistent risk factors for serious infections have been underlying disease severity and concomitant use of corticosteroids and immunosuppressive therapies. By adequately controlling disease activity and minimizing corticosteroid use, a strategy using effective medications to induce remission may be associated with a lower risk of serious infections as compared to using an ineffective but potentially 'safer' medication.

Question 3.—In adult outpatients with moderate-severe UC, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of clinical remission?

Key Message #1: In adult outpatients with steroid-dependent moderate-severe UC, the benefit of thiopurines for induction of remission is uncertain (*very low quality evidence*). However, in patients with steroid-induced remission, azathioprine may be effective for maintenance of remission (*low quality evidence*).

Key Message #2: In adult outpatients with steroid-dependent moderate-severe UC, the benefit of methotrexate for induction and maintenance of remission is uncertain (*very low quality evidence*).

Effect Estimates and Quality of Evidence:

Thiopurines for moderate-severe UC, induction of clinical remission: We identified 5 trials comparing thiopurines vs. placebo (3 trials),[80–82]. or 5-ASA (2 trials)[83, 84]for achieving corticosteroid-free clinical remission. Thiopurines were dosed based on body weight (2–2.5mg/kg azathioprine or 1.5mg/kg mercaptopurine) in all trials, except one in which azathioprine was used at a dose of 1.5mg/kg/d. In all these trials, patients had active UC, with moderate to severe disease activity, and were on corticosteroids at time of trial entry. In 4 of 5 trials, patients had steroid-dependent UC wherein patients were unable to taper below 10–20mg/d prednisone without clinical relapse. Trials analyzed the ability to achieve steroid-free clinical remission, using variable disease activity indices. Timing of assessment of outcome varied from 4 weeks to 52 weeks. Based on a meta-analysis, patients treated with thiopurines were associated higher rates of achieving steroid-free clinical remission as compared to patients treated with placebo or 5-ASA (RR, 1.25; 95% CI, 1.01–1.56) (eFigure 3).

Quality of Evidence: The overall body of evidence supporting thiopurines for induction of clinical remission was rated as very low quality (Table 6). There was serious risk of bias due

to inadequate blinding of patients and outcome assessors. In addition, there was serious indirectness, since these trials did not truly assess induction of remission, but rather the ability to achieve steroid-free clinical remission, over a wide range of time, using a variety of disease activity indices (with definitions inconsistent with modern definitions of remission). It is possible that in the majority of patients, corticosteroids were responsible for inducing remission, whereas thiopurines helped maintain corticosteroid-free remission. Finally, evidence was rated down for serious imprecision due to low event rate, and imprecise estimates in placebo-controlled trials.

Thiopurines for moderate to severe UC, maintenance of clinical remission: We identified 7 trials comparing thiopurines vs. placebo (4 trials),[80, 82, 85, 86] or 5-ASA (3 trials),[84, 87, 88] addressing ability of thiopurines to maintain remission. In these trials, maintenance of remission was either defined as prevention of relapse after steroid-induced remission (5 trials) or as ability to maintain sustained steroid-free remission in patients on prolonged thiopurines (2 trials), assessed between 6–18 months. Some trials contributed to addressing both induction and maintenance of remission. In this analysis, in contrast to the previous analysis on efficacy of thiopurines to induce/achieve steroid-free remission, we only included patients who had inactive disease at start of follow-up. In a meta-analysis of these studies, thiopurines were significantly more effective than no thiopurines for prevention of relapse after achieving remission (RR, 0.61; 95% CI, 0.49–0.77); these effects were consistent and significant in subgroups of trials comparing thiopurines vs. placebo and vs. 5-ASA (eFigure 4).

Quality of Evidence: The overall body of evidence supporting thiopurines over no thiopurines for maintenance of remission was rated as low quality (Table 6). There was concern for risk of bias due to lack of adequate blinding. Additionally, due to low event rate, evidence was also rated down for imprecision.

Methotrexate for moderate to severe UC, induction of clinical remission: We identified three trials comparing oral or subcutaneous methotrexate vs. placebo (2 trials)[89, 90] or 5-ASA,[84] for achieving corticosteroid-free remission in patients with steroid-dependent UC. In two trials, patients had active disease at baseline on corticosteroids. In one of the largest trials of subcutaneous methotrexate (METEOR), all patients were on corticosteroids 10–40mg/d at entry, with or without active disease. Primary outcome for all trials was corticosteroid-free clinical remission, assessed between weeks 12–30; while MCS was used for all trials, the cut-offs for defining remission were variable, ranging from <3 to <6. On meta-analysis, there was no significant difference in the rates of achieving corticosteroid-free remission in patients receiving methotrexate vs. no methotrexate (RR, 1.31; 95% CI, 0.89–1.94) (eFigure 5); these results were also non-significant in trial comparing subcutaneous methotrexate vs. placebo in the METEOR trial (RR, 1.61; 95% CI, 0.83–3.15).

Quality of Evidence: The overall body of evidence was rated as very low quality due to indirectness (different modes of administering methotrexate, different definitions of clinical remission, inability to truly assess induction of remission since the majority of patients were

receiving corticosteroids for inducing remission), and for very serious imprecision (very wide confidence intervals crossing unity) (Table 7).

Methotrexate for moderate to severe UC, maintenance of remission: We included 3 trials comparing oral or subcutaneous methotrexate vs. placebo (2 trials)[90, 91] or 5-ASA (1 trial) for maintenance of remission.[84] Mate-Jiminez *et al* evaluated the risk of relapse while on oral methotrexate vs. 5-ASA over 56 weeks, in a subset of patients who achieve corticosteroid-free remission at end of 30 week induction study. In contrast, MERIT-UC was methotrexate withdrawal study in which patients who achieved corticosteroid-free remission by week 16 on open-label methotrexate, were randomized either to continuing vs. stopping methotrexate. On meta-analysis, there was no difference in risk of relapse in patients with moderate-severe UC in corticosteroid-free remission, between patients treated with methotrexate vs. no methotrexate (RR, 1.01; 95% CI, 0.79–1.29) (eFigure 6).

Quality of Evidence: The overall body of evidence was rated as very low quality due to indirectness (different modes of administering methotrexate) and very serious imprecision (very wide confidence interval, with summary estimate at unity) (Table 7).

Potential Harms of Intervention: Risks of side effects with thiopurines and methotrexate have been summarized above. Besides the direct risks associated with these therapies, risks associated with use of ineffective therapies and delay in initiation of more effective therapies also need to be considered when evaluating potential harms of intervention.

Discussion: Based on evidence presented above, thiopurine monotherapy may be effective for maintaining corticosteroid-free remission in patients with UC; however, the benefit of thiopurines for induction of remission is unclear. Thiopurines have a slow onset of action, and so they have conventionally been used as maintenance agents, rather than induction agents. In the trials of thiopurine therapy in patients with active UC, outcomes were usually assessed 26 weeks or beyond (in 3 trials), in contrast to modern trials and clinical practice of induction therapy where response to induction therapy is generally assessed within 8–12 weeks. Real-world cohort studies have confirmed effectiveness of thiopurines in maintaining steroid-free remission and reducing the risk of colectomy in patients with UC.[92–95]

Our analysis suggests that the benefit of methotrexate for induction and maintenance of remission is uncertain. Though differences have been suggested between oral and subcutaneous methotrexate in Crohn’s disease, in our analysis, neither oral or subcutaneous methotrexate was effective in patients with steroid-dependent UC. However, earlier trials of thiopurines in UC were conducted in biologic- and immunomodulator-naïve patients. In contrast, in METEOR and MERIT-UC, pivotal induction and maintenance trials of subcutaneous methotrexate in UC, 81% and 67% patients had prior exposure to thiopurines and/or biologic agents, respectively. Of note, in contemporary era of biologic therapies and targeted small molecules, recruitment to trials of methotrexate was challenging with METEOR recruiting 111 patients over 6 years (2007–13) and MERIT-UC recruiting 84 patients over 5 years (2012–16).

Question 4.—In adult outpatients with moderate-severe UC, is biologic monotherapy (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) or therapy with tofacitinib, superior to immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of clinical remission?

Key Message: In adult outpatients with moderate-severe UC, biologic monotherapy or tofacitinib therapy may be superior to immunomodulators for induction of remission (*very low quality evidence*). The benefit of biologic monotherapy over immunomodulator monotherapy for maintenance of remission is uncertain (*very low quality evidence*).

Effect Estimates: There are no adequately powered RCTs designed to directly compare biologic monotherapy (or tofacitinib) with immunomodulators for induction or maintenance of remission. We identified a single, three-arm RCT, UC-SUCCESS, in patients with moderate-severe UC, comparing infliximab vs. azathioprine vs. infliximab+azathioprine.[96] In this induction trial, biologic-naïve patients with moderate-severe UC, with inadequate response to prednisone within the preceding 12 weeks, were randomized to infliximab vs. azathioprine vs. infliximab+azathioprine. Patients on corticosteroids at trial entry were required to taper off corticosteroids by week 14. This study found no significant difference between infliximab monotherapy vs. azathioprine monotherapy for inducing corticosteroid-free clinical remission (MCS <3 with no individual sub-score >1, no corticosteroids at week 16) (RR, 0.96; 95% CI, 0.53–1.72). However, infliximab monotherapy was more effective than azathioprine monotherapy for inducing both endoscopic remission (RR, 1.52; 95% CI, 1.06–2.18), and for achieving clinical response (68.8% vs. 50.0%, p<0.01) at week 16. The findings of this single study should be interpreted in the context of evidence presented in Q1 and Q3. As summarized above, there is moderate quality evidence supporting the efficacy of biologic agents and tofacitinib vs. placebo for induction of remission, but no such evidence supporting the efficacy of thiopurines or methotrexate for the induction of remission.

Quality of evidence: Based on the direct and indirect evidence, the overall body of evidence supporting the use of biologic monotherapy (or tofacitinib) over immunomodulator monotherapy for induction of remission was rated as very low quality (Table 8). Evidence was rated down for risk of bias (underpowered trial that was prematurely terminated), very serious indirectness (discrepant findings based on direct and indirect evidence, direct evidence being available only for comparison of infliximab vs. azathioprine, but no other biologic agent or tofacitinib) and very serious imprecision (very wide confidence intervals when evaluating direct comparison). For maintenance of remission, in the absence of head-to-head comparison, we were unable to derive a summary estimate and comment on directionality of relationship.

Potential Harms of Intervention: As noted above, there may be a slightly higher risk of serious and opportunistic infections with biologic agents and tofacitinib vs. immunomodulators. In contrast, biologic monotherapy and tofacitinib are not consistently associated with an increase in risk of malignancy, whereas both thiopurines have been associated with a 3–6 fold increased risk of lymphoma.

Discussion: UC-SUCCESS was terminated prematurely by the sponsor, enrolling only 239 of proposed 600 patients, limiting meaningful interpretation on the comparative efficacy of infliximab vs. azathioprine.[96] Discrepant results in outcomes of clinical remission (no difference between infliximab vs. azathioprine) and endoscopic remission and clinical response (demonstrating superiority of infliximab over azathioprine) in this trial highlight the challenges in interpreting the results. Pivotal registration trials of biologic therapy and tofacitinib have confirmed superiority of these agents for induction and maintenance of remission with moderate confidence in estimates. In contrast, the benefit of thiopurines and methotrexate for induction of remission is uncertain. Therefore, indirect comparison would suggest the superiority of biologic monotherapy over thiopurine or methotrexate monotherapy for induction of remission.

Whether there is any difference between biologic monotherapy (or tofacitinib) vs. azathioprine for maintenance of remission is unclear. UC-SUCCESS was terminated before recruiting into the maintenance study. Maintenance studies of these agents do not lend themselves to indirect comparisons conceptually. However, given the lack of efficacy of methotrexate as a maintenance agent, it is likely that biologic monotherapy is more effective than methotrexate for maintenance of remission.

Question 5.—In adult outpatients with moderate-severe UC, is combination therapy of a biologic agent (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) with an immunomodulator (thiopurines or methotrexate) superior to biologic monotherapy or immunomodulator monotherapy for induction and maintenance of clinical remission?

Key Message #1: In adult outpatients with moderate-severe UC, combination therapy with infliximab + immunomodulator is probably superior to infliximab monotherapy for induction of remission (*moderate quality evidence*). Combination therapy with other biologics (other TNF-α antagonists, vedolizumab or ustekinumab) + immunomodulator may be superior to biologic monotherapy for induction of remission (*low quality of evidence*). The benefit of combination therapy of a biologic agent + immunomodulator over biologic monotherapy for maintenance of remission is uncertain (*very low quality evidence*). The benefit of combination therapy with tofacitinib and immunomodulators is currently unknown.

Key Message #2: In adult outpatients with moderate-severe UC, combination therapy with infliximab + immunomodulator is probably superior to immunomodulator monotherapy for induction of remission (*moderate quality evidence*). Combination therapy with other biologics (other TNF-α antagonists, vedolizumab or ustekinumab) + immunomodulator may be superior to immunomodulator monotherapy for induction of remission (*low quality of evidence*). The benefit of combination therapy over immunomodulator monotherapy for maintenance of remission is uncertain (*very low quality evidence*).

Effect estimate and Quality of Evidence:

Combination Therapy vs. Biologic monotherapy: We identified a single three-arm, double-blind, double-dummy RCT, UC-SUCCESS in patients with moderate-severe UC, comparing infliximab vs. azathioprine vs. infliximab+azathioprine, for induction of

remission.[96] In this trial, the combination of infliximab+azathioprine had significantly higher efficacy than infliximab monotherapy for induction of corticosteroid-free remission at week 16 (RR, 1.78; 95% CI, 1.08–1.94) (eFigure 7). However, difference between rates of achieving endoscopic remission (combination therapy vs. infliximab monotherapy: 63% vs. 55%, p=0.30) and clinical response (77% vs. 69%, p=0.51) between combination therapy vs. infliximab monotherapy were not significant. No trials specifically comparing other non-infliximab TNF-α antagonists, vedolizumab or ustekinumab with immunomodulators vs. monotherapy with biologic agent were identified. Similarly, no trials comparing a methotrexate-based combination therapy for UC were identified.

As noted above, though UC-SUCCESS was conceived as an induction and maintenance trial, it was terminated prematurely by the sponsor. Hence, we have very limited data to inform the comparative efficacy of combination therapy vs. biologic monotherapy for maintenance of remission. In a retrospective French cohort study of 82 patients in sustained corticosteroid-free clinical remission on combination therapy of infliximab and azathioprine, a significantly lower risk of relapse was observed in those who continued combination therapy vs. those who de-escalated to infliximab monotherapy.[97]

Quality of Evidence: The overall body of evidence supporting infliximab + immunomodulators over infliximab alone in patients with moderate-severe UC was rated as moderate quality, rated down for imprecision due to low event rate (Table 9). Due to indirectness in extrapolating evidence from infliximab to other TNF-α antagonists, vedolizumab or ustekinumab, we opted to rate the quality of evidence supporting TNF-α antagonists, vedolizumab or ustekinumab + immunomodulator over TNF-α antagonists, vedolizumab or ustekinumab monotherapy as low quality.

With the retrospective nature of the observational study evaluating combination therapy vs. infliximab monotherapy for maintenance of remission and small sample size, overall body of evidence supporting combination therapy over infliximab monotherapy for maintenance of remission was rated as very low quality.

Combination Therapy vs. Immunomodulator monotherapy: Based on the same UC-SUCCESS trial, combination therapy of infliximab and azathioprine was superior to azathioprine monotherapy for achieving corticosteroid-free remission at week 16 (RR, 1.70; 95% CI, 1.04–2.78) (eFigure 7).[96] Similar favorable effects of combination therapy were observed in achieving endoscopic remission and clinical response. We did not identify any trials or observational studies comparing combination therapy vs. immunomodulator monotherapy for maintenance of remission.

Quality of Evidence: The overall body of evidence supporting infliximab + immunomodulators over infliximab monotherapy in patients with moderate-severe UC was rated as moderate quality, rated down for imprecision due to low event rate (Table 10). This key trial examined only infliximab, so these results may or may not be properly extrapolated to other TNF-α antagonists, vedolizumab or ustekinumab. Therefore, we rated down the evidence further to low quality for other biologic medications due to indirectness.

Potential Harms of Intervention: As noted above, TNF-α antagonist monotherapy may be associated with an increased risk of serious and opportunistic infections as compared to immunomodulator monotherapy. There is inadequate evidence to inform comparative safety of vedolizumab, tofacitinib or ustekinumab vs. immunomodulators, though by virtue of its gut specificity, monotherapy with vedolizumab may carry lower risks of adverse effects. These direct safety concerns should be interpreted in the context of higher efficacy in inducing corticosteroid-free remission with combination therapy, potentially avoiding repeated courses of corticosteroids, hospitalization, surgery, and persisting on index biologic therapy by avoidance of immunogenicity.

Discussion: Combining biologic agents with immunomodulators increases efficacy through several potential mechanisms. First, immunomodulators have their independent efficacy in patients with UC, which may add to the benefits observed with biologics. Second, immunomodulators have been consistently shown to decrease the risk of immunogenicity to biologic agents, and may increase trough concentrations of these agents.[98] However, direct comparison with drugs other than infliximab are lacking, and the rates of immunogenicity with adalimumab, golimumab, vedolizumab and ustekinumab are lower than with infliximab. Therefore, the benefit of combination therapy with these agents in terms of mitigating antibody formation may be less than with infliximab. There also are very limited data on the comparative efficacy of combination therapy over monotherapy with biologics or immunomodulators for maintenance of remission as noted above, so the evidence regarding maintenance of remission was rate as very low quality.

Question 6.—In adult outpatients with moderate-severe UC, is upfront use of biologics and/or immunomodulator therapy superior to step-up therapy (acceleration to biologic and/or immunomodulator therapy only after failure of 5-ASA) for induction and maintenance of remission?

Key Message: Early use of biologic agents and/or immunomodulator therapy may be more effective than gradual step-up therapy in achieving remission in adult outpatients with moderate-severe ulcerative colitis (*very low quality evidence*).

Effect estimates: We did not identify any trials comparing a strategy of upfront use of biologics and/or immunomodulator therapy vs. gradual step-up therapy in patients with moderate-severe UC. We also did not identify any trials comparing the efficacy of biologic agents therapy vs. 5-ASA for patients with moderate-severe UC. There are, however, three trials that compared thiopurines in this population.[84, 87, 88] Based on a meta-analysis of these studies, patients treated with thiopurines achieved higher rates of corticosteroid-free clinical remission as compared to patients treated with 5-ASAs. Furthermore, as demonstrated previously, biologic agents may be more effective than immunomodulators for induction of remission based on clinical trials, so by extension, biologic therapy would be more effective than 5-ASA for induction of remission in patients with moderate-severe UC. We also know that 5-ASAs are not indicated for the treatment of moderate-severe UC, nor have they been demonstrated to be steroid-sparing agents in UC. Based on this indirect evidence, it follow that delaying treatment of moderate-severe UC with biologic therapy or immunomodulators to treat with 5-ASA drugs may be detrimental, both because 5-ASAs would not work as

primary therapy and because use of these drugs will introduce a treatment delay impairing quality of life and increasing risk of complications.

Quality of Evidence: Based on serious indirectness of the evidence with, unclear estimates of magnitude of benefit, we rated the quality of evidence as very low quality.

Potential Harms of Intervention: Risks associated with biologic or immunomodulator therapy have been outlined earlier and may be greater than those associated with 5-ASA therapy. However, these risks should be interpreted in the context of risks of UC-related complications, including colectomy, hospitalization, persistent disease activity resulting in inferior quality of life, if step-up therapy is used.

Discussion: Inadequately controlled UC is associated with an increased risk of colectomy, hospitalization, corticosteroid use, as well as long-term risk of colorectal cancer. Similar to Crohn's disease, UC is also a progressive disease that can result in bowel damage, in the form of proximal extension, stricturing, pseudopolyposis, dysmotility, anorectal dysfunction, and impaired permeability.[99] Hence, risk-congruent therapy is warranted to minimize risk of short- and long-term complications and bowel damage. Unfortunately, prediction models to identify patients at high risk of complications or 'disease severity' indices have not been well validated. Ideally, evidence regarding top-down vs. step-up therapy would be best informed by a pragmatic RCT comparing outcomes in patients assigned to risk-congruent therapy vs. conventional management. In the absence of these data, based on indirect evidence, it is likely that step-up therapy using 5-ASAs first in patients with moderate-severe UC may be detrimental.

Question 7.—In adult outpatients with moderate-severe UC failing 5-aminosalicylates, who are now to be treated with immunomodulators, biologic therapy or tofacitinib, is continuing 5-ASAs superior to stopping the 5-ASAs for inducing and maintaining remission?

Key Message: In adult outpatients with moderate-severe UC, who have failed 5-ASAs, and have escalated to therapy with biologic agents, tofacitinib and/or immunomodulators, there may be no benefit to continuing 5-ASAs over stopping 5-ASAs (*low quality evidence*).

Effect estimate: Mantzaris et al randomized patients with moderate to severe UC, in corticosteroid-free clinical, endoscopic and histologic remission on azathioprine+olsalazine, to either continuing azathioprine+olsalazine (0.5mg TID) vs. azathioprine alone.[100] Over the course of two years, there were no observed differences in risk of relapse severe enough to merit corticosteroid use (RR, 1.02; 95% CI, 0.77–1.34). We did not identify any studies directly addressing the addition of withdrawal of 5-ASA therapy in patients with moderate-severe UC also being treated with biologic agents or tofacitinib, so we relied on indirect evidence from sub-group analyses of the RCTs examining the efficacy of these drugs.[101] In these trials, Singh and colleagues compared rates of induction and maintenance of clinical remission between patients who were or were not on concomitant 5-ASAs at time of trial entry. All patients in these trials had moderate to severe active disease, despite prior 5-ASA exposure. The patients in these trials had to maintain their baseline medications, so they

could not stop or start 5-ASA during the course of the trial. Based on a meta-analysis, combining two trials of infliximab (ACT-1 and −2), one induction trial of golimumab (PURSUIT-SC), one trial of adalimumab (ULTRA-2) and one phase II trial of tofacitinib, there was no differences in rates of inducing clinical remission in patients with active disease on concomitant 5-ASA vs. no concomitant 5-ASA: RR, 0.94; 95% CI, 0.74–1.18) (eFigure 8). Similar results were obtained in trials of maintenance therapy. Based on three trials of biologic therapy (ACT-1, −2 and PURSUIT-M), and one trial of thiopurines, there was no differences in risk of maintaining remission between those who were on concomitant 5-ASAs vs. those who were not on concomitant 5-ASA (RR, 0.92, 95% CI, 0.78–1.09).

Quality of Evidence: The overall body of evidence supporting lack of benefit of continuing vs. stopping 5-ASAs in patients with moderate-severe UC being treated with biologic agents, tofacitinib and/or immunomodulators, after prior exposure to and failure of 5-ASA, was rated as low quality for both induction and maintenance of remission (Table 11). Evidence was rated down due to imprecision (low event rate), and for indirectness.

Potential Harms of Intervention: 5-ASAs are generally safe medications, with very low rates of idiosyncratic serious or life-threatening complications. There are rare reports of allergic interstitial nephritis, pancreatitis, pericarditis, myocarditis, and pneumonitis. In contrast, sulfasalazine has higher risk of side effects.[102, 103] Between 10 and 45% patients treated with sulfasalazine may develop dose-related adverse effects, including nausea, dyspepsia, headache and fatigue with sulfasalazine. Sulfasalazine also been associated with serious cutaneous reactions such as toxic epidermal necrolysis and Stevens Johnson syndrome, primarily attributed to the sulfapyridine moiety.

Discussion: We relied on a combination of direct evidence in patients on thiopurines, and indirect evidence in biologic-treated patients, to determine the efficacy of continuing vs. stopping 5-ASA patients in patients who escalate therapy after failing 5-ASA. Due to the short duration of follow-up in clinical trials, we were not able to study the impact of concomitant 5-ASAs on longer-term risk of disease-related complications including surgery and development of colorectal neoplasia. A single retrospective cohort study of 82 patients with UC in remission on azathioprine did not find that, concomitant therapy with 5-ASA was associated with lower risk of clinical relapse (surgery or need for rescue therapy) over a median follow-up of 4.3y.[104] One proposed benefit of long-term 5-ASA use is a potential chemoprevention effect against colorectal cancer, but this remains unproven.[105] While large observational studies and meta-analyses have variably suggested that UC patients treated with 5-ASA have lower risk of developing colorectal cancer, recent evidence suggests that chronically active disease is a strong risk factor for developing neoplasia, and sustained remission is a protective factor against colorectal cancer regardless of therapy used that achieves this outcome.[106]

Pharmacological management of hospitalized patients with acute severe ulcerative colitis

Question 8.—In hospitalized patients with ASUC, what is the optimal dose of intravenous methylprednisolone for decreasing risk of colectomy?

Key Message: In hospitalized patients with ASUC, methylprednisolone dose >60mg/d, or equivalent if another corticosteroid is used, may not be superior to lower doses of corticosteroids (40–60mg/d) in reducing risk of colectomy (*very low quality evidence*).

Effect Estimate: We did not identify any trials in hospitalized patients with ASUC comparing different dosing regimens of corticosteroids. We relied on a systematic review evaluating the risk of colectomy in patients with ASUC, in which the authors evaluated risk factors associated with colectomy.[107] In this analysis of 24 cohort studies, mean methylprednisolone was 68mg, ranging from 40–100mg/d; only 3 studies used a dose <60mg/d. On meta-regression, controlling for baseline disease severity, there was no correlation between corticosteroid dose and risk of colectomy (R^2<0.01).

Quality of Evidence: Since evidence was derived from a meta-regression of cohort studies, without head-to-head comparison of different studies, it was deemed to be very low quality.

Potential Harms of Intervention: High dose corticosteroids are associated with increased risk of serious infections, poor wound healing as well as myriad acute side effects including mood changes, irritability, psychosis, weight gain, increased appetite, and others.[108] In contrast, if dose of corticosteroids is inadequate to induce a clinical response in patients with ASUC, the patient may be deemed to have corticosteroid-refractory ASUC, putting patient at higher risk for colectomy.

Discussion: Intravenous corticosteroids are the first-line therapy for hospitalized patients with ASUC. However, we did not identify any studies directly comparing different dosing regimens of corticosteroids. Instead, we had to rely on indirect evidence from cohort studies. We found a wide variability in the doses of corticosteroids used. A meta-regression across these studies failed to confirm any benefit with use of >60mg/d of intravenous methylprednisolone or equivalent. Corticosteroids may be administered either as an IV bolus in single or divided doses, or as a continuous infusion. In one clinical trial, there was no difference in rates of achieving clinical remission by day 7 in patients who received equivalent doses of methylprednisolone either as continuous infusion vs. bolus (50% vs. 50%).[109] Optimal duration of intravenous corticosteroids has also not been compared in clinical trials. Several prediction models have been developed to identify factors associated with colectomy. In these models, re-evaluation is typically recommended within 3 to 7 days of starting corticosteroids, and failure of clinical and biochemical improvement is associated with high risk of colectomy.[12] Seo and colleagues estimated that failure to respond to intravenous corticosteroids within 1 week was associated with >60% risk of colectomy in patients with ASUC.[110] Hence, it seems reasonable that, in the absence of high quality evidence, that a trial of intravenous corticosteroids in patients with ASUC should be limited to 7 days, with low threshold for escalation to rescue therapy or colectomy in patients who have inadequate response to intravenous corticosteroids by day 3 to 5.

Question 9.—In hospitalized patients with ASUC, without a gastrointestinal infection, is adjunctive antibiotic therapy more effective than no antibiotic therapy for decreasing risk of colectomy?

Key Message: In hospitalized patients with ASUC without gastrointestinal infections, adjunctive antibiotics may not be effective in decreasing risk of colectomy (*very low quality of evidence*).

Effect Estimates: We identified 4 RCTs performed between 1985–2001, comparing the effect of adding antibiotics to corticosteroids (3 intravenous, 1 oral corticosteroids) to treat ASUC.[111–114] Different antibiotics were used in different trials for 5–10 days, including intravenous metronidazole, intravenous ciprofloxacin, oral vancomycin and combination of intravenous metronidazole and tobramycin. All trials confirmed negative testing for *Clostridium difficile* and had negative stool cultures. On meta-analysis, the addition of antibiotics was not associated with decreased risk of in-hospital colectomy (RR, 0.79; 95% CI, 0.46–1.35) (eFigure 9). One trial by Dickinson *et al* suggested a protective benefit, whereas all other trials were negative.[112] While all other trials used antibiotics predominantly directed against gastrointestinal microbiota, Dickinson *et al* used vancomycin. Though their trial, ruled out *Clostridium difficile* infection using a cell cytotoxicity assay using Hep-2 monolayers, the sensitivity of this test is low as compared to more modern methods of detecting C. difficile, missing as many as 40% of cases.[115] Therefore, the benefits of the oral vancomycin might relate to treatment of unrecognized C difficile infection in their study population or prevention of this infection. On exclusion of the trial by Dickinson et al, the summary estimate for the benefits of adjunctive antibiotics was near unity (RR, 0.95; 95% CI, 0.55–1.64).

Quality of Evidence: Overall body of evidence evaluating the impact of adjunctive antibiotics in decreasing risk of colectomy in patients with ASUC was rated as very low quality (Table 12). These trials were at serious risk of bias because of poor methodology, had very high imprecision, and there was inconsistency with diverse antibiotics being used.

Potential Harms of Intervention: Short-term course of antibiotics are associated with different minor and infrequently serious side effects and may increase the risk of developing *Clostridium difficile*.

Discussion: Antibiotics are frequently used in hospitalized patients with ASUC, often without any clear evidence of gastrointestinal infections. Three trials failed to show any benefit of adjunctive antibiotics, whereas one trial of oral vancomycin suggested benefit. However, in this trial, an insensitive test was used to rule out Clostridium difficile, and it is possible that benefit could be attributed to treating missed infections with this organism. In a retrospective cohort study on patients with ASUC, Gupta and colleagues observed that combination of antibiotics with intravenous corticosteroids was associated with lower need for in-hospital rescue therapy, though there was no difference in length of stay, in-hospital surgery, re-hospitalization or surgery within 1 year.[116]

Question 10.—In hospitalized patients with ASUC, refractory to intravenous corticosteroids, what is the efficacy of TNF-α antagonists (infliximab, adalimumab, golimumab), vedolizumab, tofacitinib, immunomodulators, cyclosporine or tacrolimus for decreasing risk of colectomy?

Key Message: In hospitalized patients with ASUC, refractory to intravenous corticosteroids, infliximab is probably effective (*moderate quality evidence*) and cyclosporine may be effective in decreasing risk of colectomy (*low quality evidence*). The benefit of tacrolimus for decreasing risk of colectomy is uncertain (*very low quality of evidence*). There are very limited data to inform the efficacy of other interventions (adalimumab, golimumab, vedolizumab, tofacitinib and immunomodulators) in this patient population.

Effect estimates and Quality of Evidence:

Infliximab vs. placebo: Based on a single small RCT of 45 patients in patients with ASUC, refractory to intravenous corticosteroids, infliximab was more effective than placebo in decreasing the risk of colectomy within 90 days of hospitalization (7/24 vs. 14/21; RR, 0.44; 95% CI, 0.22–0.87).[117] Of note, patients in these trials received only a single dose of 5mg/kg infliximab, without subsequent induction or maintenance doses.

Quality of evidence: The overall body of evidence supporting infliximab over placebo for decreasing the risk of colectomy in this patient population was rated as moderate quality (Table 13). Evidence was rated down for imprecision due to low event rate. Though only a single dose of infliximab was used, evidence was not rated down for indirectness. It is expected that if the standard induction and maintenance dosing regimen of infliximab was used, the beneficial effect over placebo would have persisted and may even have been stronger.

Cyclosporine vs. placebo: In a single small RCT comparing intravenous cyclosporine (4mg/kg) vs. placebo in corticosteroid-refractory patients with ASUC, there was a trend towards lower risk of in-hospital colectomy in patients treated with cyclosporine (3/11 vs. 4/9; RR, 0.61; 95% CI, 0.18–2.01).[118] In a subsequent RCT comparing different doses of intravenous cyclosporine, Van Assche *et al* compared 2mg/kg/d vs. 4mg/kg/d in decreasing risk of colectomy within 2 weeks of hospitalization for ASUC in corticosteroid-refractory patients.[119] There was no significant difference between the two doses (2mg/kg/d vs. 4mg/kg/d: 3/35 vs. 5/38; RR, 0.65; 95% CI, 0.17–2.53).

Quality of evidence: Evidence was rated down for very serious imprecision, and rated as low quality (Table 13).

Tacrolimus vs. placebo: Two trials of oral tacrolimus in hospitalized patients with corticosteroid-dependent or corticosteroid-refractory UC.[120, 121] In these trials, medication administration and outcome assessment was performed at 2 weeks, and clinical response (at least 4 point improvement in disease activity index) was the primary end point, None of the patients underwent colectomy. Overall, patients treated with tacrolimus were significantly more likely to achieve clinical response as compared to placebo (37/72 vs. 6/50; RR, 4.34; 95% CI, 1.95–9.67). When analysis was limited to patients where tacrolimus dosing was targeted to achieve a trough of 10–15ng/ml, similar effect size was obtained (RR, 4.74; 95% CI, 2.16–10.41).

Quality of Evidence: The evidence was rated down due to risk of bias (unclear sequence generation and allocation concealment), imprecision (low event rate) and serious indirectness (mix of patients with corticosteroid-dependent and corticosteroid-refractory patients, reporting only clinical response as outcome, probably different patient population than other trials of corticosteroid-refractory ASUC considering none of the patients underwent colectomy). Hence, the overall body of evidence supporting tacrolimus over placebo for decreasing risk of colectomy in patients with corticosteroid-refractory ASUC was rated as very low quality.

Other medications: We did not identify any trials or prospective cohort studies of adalimumab, golimumab, vedolizumab, tofacitinib or immunomodulators as primary therapy in hospitalized patients with corticosteroid-refractory ASUC.

Potential Harms of Intervention: Corticosteroid-refractory patients with ASUC intrinsically are at high-risk of disease-related complications, such as colectomy, malnutrition, serious infections and venous thromboembolism. Emergent colectomy in these patients carries a higher mortality than elective colectomy (5.3% vs. 0.7%).[122] Use of immunosuppressive therapies in these patients increases the risk of infections, perhaps to a greater degree than in outpatients due to intrinsically higher susceptibility. Risks associated with infliximab have been summarized earlier. Calcineurin inhibitors (cyclosporine and tacrolimus) have a narrow therapeutic window and drug interactions.[123] Rare but serious toxicity includes seizures, hypomagnesemia and opportunistic infections such as *Pneumocystis* or *Aspergillus*. Other adverse effects include paresthesias, hypertension, hypokalemia and hypertrichosis. Based on a meta-analysis of 10 studies with 314 patients, sequential therapy, either adding cyclosporine in patients with inadequate response to infliximab, or vice versa, is associated with a significantly higher risk of adverse events (23%), serious infections (6.7%) and mortality (1%).[124]

Discussion: Approximately 30% patients with ASUC may become corticosteroid-refractory and require medical or surgical rescue therapy. Short-term colectomy rate in these patients is ~25–30%.[4] Based on evidence presented above, infliximab is probably effective and cyclosporine may be effective in decreasing short-term risk of colectomy in corticosteroid-refractory patients with ASUC. Oral tacrolimus, targeting a trough concentration of 10–15ng/ml, may also be effective in inducing clinical response in the short-term, which probably translates into lower risk of colectomy.

Post-hoc analysis of pivotal phase III trials of tofacitinib in outpatients with moderate-severe UC suggest that ~29–32% patients may experience decrease in stool frequency and rectal bleeding within 3 days of initiation of therapy.[125] Other biologics have not been specifically evaluated in the setting of ASUC. Vedolizumab, an anti-integrin agent, has a relatively slower onset of action particularly in patients with prior exposure to other biologics, and may not be effective by itself in hospitalized patients with ASUC.[126] However, in a recent case series, calcineurin inhibitors have been used as a bridge to vedolizumab in corticosteroid-refractory patients with UC (hospitalized or outpatients) who have previously been exposed to infliximab.[127] Calcineurin inhibitors were used as induction agents for 6–12 weeks, simultaneously with vedolizumab. In this cohorts, ~55% patients achieved clinical

response by week 14; colectomy-free survival at 1 year was 68%. Immunomodulators have a slow-onset of action, and are very unlikely to be effective as monotherapy in patients with ASUC.

Question 11.—In hospitalized patients with acute severe ulcerative colitis, refractory to intravenous corticosteroids, is infliximab superior to cyclosporine for decreasing risk of colectomy?

Key Message: In hospitalized patients with ASUC, refractory to intravenous corticosteroids, infliximab and cyclosporine may be equally effective in decreasing risk of colectomy (*low quality evidence*).

Effect Estimates: Based on two trials, there was no significant difference in short-term risk of colectomy between standard dose induction therapy with infliximab and cyclosporine in hospitalized patients with corticosteroid-refractory ASUC (RR, 1.00; 95% CI, 0.72–1.40) (eFigure 10).[128, 129] In the long-term, over 12 months, risk of colectomy was slightly lower in patients treated with infliximab vs. cyclosporine, though this was not statistically significant (RR, 0.84; 95% CI, 0.66–1.08). Importantly, in these trials, randomized treatment was offered for 12–14 weeks, after which treatment decisions were deferred to treating physicians.

Quality of evidence: Overall the body of evidence comparing infliximab vs. cyclosporine for decreasing risk of short-term colectomy in hospitalized patients with corticosteroid-refractory ASUC was rated as low quality (Table 14). Both trials were open-label, with a pragmatic design of one of the larger trials; as a result, evidence was rated down for risk of bias. Due to wide confidence intervals, evidence was rated for imprecision.

Potential harms of intervention: As discussed earlier, both infliximab and cyclosporine increase risk of serious and opportunistic infections, particular in this refractory population with ASUC. In both included trials, there was no significant difference in the risk of serious, non-IBD-related adverse events (infliximab vs. cyclosporine: RR, 1.49; 95% CI, 0.87–2.55). On meta-analysis of non-randomized comparative studies, Narula and colleagues also observed no significant differences in rates of serious adverse events (RR, 0.41; 95% CI, 0.08–2.09), or mortality (RR, 1.37; 95% CI, 0.31–6.10).[124] Though one of the proposed advantages of cyclosporine is it's short half-life which allows of rapid washout in case surgery is warranted, no significant differences in rates of post-operative complications have been observed (RR, 1.05; 95% CI, 0.40–2.77).

Discussion: Infliximab and cyclosporine have been the most commonly studied interventions in patients with corticosteroid-refractory ASUC. The pivotal CYSIF head-to-head trial by Laharie et al was designed as a superiority trial favoring cyclosporine, and was powered to detect a 30% difference in failure rate between cyclosporine and infliximab groups.[128] However, the study failed to identify any significant difference in rates of colectomy or treatment failure (a composite outcome of the study, defined as the presence of any of the 6 following criteria: absence of clinical response at day 7, relapse between day 7 and 98, absence of corticosteroid-free remission at day 98, a severe adverse event leading to

treatment interruption, colectomy, or death) between cyclosporine and infliximab (60% vs. 54%). In the subsequent CONSTRUCT trial comparing cyclosporine vs. infliximab, the primary outcome was quality-adjusted survival.[129] In this trial, there was no difference in quality-adjusted survival or quality of life over 1–3 year of follow-up after randomization to 12-week randomized therapy. Importantly, in both trials, cyclosporine dose was monitored to achieve a narrow therapeutic window between 100–250 ng/ml; in contrast, only standard induction dosing of infliximab was used, without therapeutic drug monitoring or attempts at treatment optimization.

Long-term follow-up of these trials also suggest similar findings. Over a median follow-up of 4.5 years of participants in the CYSIF trial, 1- and 5-year colectomy free survival was 70.9% and 61.5% in patients treated with cyclosporine initially and 69.1% and 65.1%, respectively, in patients randomized to infliximab (p=0.97).[130] Interestingly, after the initial randomization period, 1- and 5-year cumulative use of infliximab in cyclosporine-treated patients was 45.7% and 57.1%, respectively; in contrast, only 4 infliximab-treated patients switched to cyclosporine. Similarly, in the CONSTRUCT trial, patients randomized to cyclosporine only continued cyclosporine for 6 months, and a significant proportion were switched to infliximab after completion of study. In contrast, observational cohort studies suggest that infliximab may be superior to cyclosporine in decreasing risk of colectomy. On meta-analysis to these studies, Narula and colleagues observed a lower risk of 3-month colectomy in patients treated with infliximab (OR, 0.53; 95% CI, 0.22–1.28) or 12-month colectomy (OR, 0.42; 95% CI, 0.22–0.83).[4] Based on these data, infliximab and cyclosporine may have comparable efficacy in decreasing short-term risk of colectomy, and based on follow-up of trial participants, an initial strategy of treating with infliximab vs. cyclosporine may not modify the long-term risk of colectomy. However, there is higher long-term persistence on infliximab therapy, whereas most patients use cyclosporine for a short duration of time, and are then transitioned to other long-term maintenance therapies, which often includes infliximab.

Question 12.—In hospitalized patients with ASUC being treated with infliximab, is routine administration of intensive dosing regimens superior to standard dosing regimens in decreasing risk of colectomy?

Key Message: In hospitalized patients with acute severe ulcerative colitis being treated with infliximab, the benefit of routine administration of accelerated dosing regimens over standard dosing regimens is uncertain (*very low quality evidence*).

Effect Estimates: We did not identify any clinical trials comparing different infliximab dosing regimens in hospitalization patients with ASUC. Five observational studies compared outcomes in patients hospitalized with ASUC being treated with different infliximab regimens (eTables 5 and 6).[131–135]In these studies, intensive dosing was defined as either shortened interval between infliximab doses (‘dose stacking’) and/or induction with higher dose (10mg/kg) either upfront or at time of dose stacking. Across studies, there was no standard protocol to determine which infliximab regimen to use when, but rather most decisions were at the discretion of the treating physician. Dose stacking was performed based on inadequate response to initial regimen, rather than being pre-determined. On meta-

analysis of these five studies with 515 patients, there was no difference in short-term risk of colectomy between intensive infliximab dosing regimen vs. standard infliximab dosing regimen (RR, 1.61; 95% CI, 0.74–3.52), with considerable heterogeneity. When the analysis was restricted to studies that used propensity score matching methods to improve comparability of groups, there was still no significant difference between groups (RR, 0.79; 95% CI, 0.24–2.61). However, in two studies, upfront induction with higher dose (10mg/kg infliximab) was superior to dose stacking with standard doses (5mg/kg) with lower risk of colectomy (RR, 0.24; 95% CI, 0.08–0.68).

Quality of evidence: The overall body of evidence supporting routine use of intensive infliximab dosing regiments vs. standard infliximab dosing for patients hospitalized for ASUC was rated as very low quality. These observational studies were rated down further due to risk of bias (intrinsic confounding by disease severity) and imprecision and inconsistency in effect estimates.

Potential harms of intervention: There is no consistent association between intensive infliximab dosing regimens, possibly leading to higher infliximab drug concentrations, and serious adverse events. Association between pre-operative infliximab and post-operative complications in a subset of patients who undergo colectomy is also inconsistent.[136–138]

Discussion: Patients with corticosteroid-refractory ASUC have a high inflammatory burden, and may develop a protein-losing enteropathy leading to an accelerated consumption and excessive fecal wasting of infliximab resulting in low serum concentrations, and potentially increased risk of immunogenicity.[139] Given a clear exposure-response relationship for infliximab in patients with IBD, intensive infliximab dosing regimens have been used in patients with ASUC. However, most observational studies are limited by selective use of intensive dosing regimens in patients with inadequate response to standard induction dose, resulting in confounding by disease severity. Patients treated with intensive regimens generally had higher C-reactive protein, lower albumin and were more likely to have severe endoscopic activity as compared to patients treated with standard dosing regimens. There are no validated prediction models to identify patients at high risk of drug clearance, or dosing calculators to allow personalization of dosing regimens upfront, which limits inferences made from current retrospective studies.

EVIDENCE-TO-DECISION FRAMEWORK

Patients' Values and Preferences of UC Therapy

Medication efficacy vs. risk: In a discrete choice experiment study of 202 patients with IBD (125 patients with UC), Bewtra and colleagues observed that to delay relapse by 5 years, patients were willing to accept up to a 28% chance of having a serious infection and 1.8% chance of having a lymphoma; these maximal acceptable risk rates were higher in patients with UC than Crohn's disease.[140] These rates vary depending on disease state – patients with active disease are willing to accept comparatively less risk than patients with no active symptoms to achieve a given improvement in time to relapse. For example, to delay a relapse for 1.5 years, patients currently in remission would be willing to accept a

15.6% risk of infection and 1.1% risk of lymphoma, whereas patients currently experiencing symptoms were willing to accept only 8.5% risk of infection and 0.5% risk of lymphoma.

Medications vs. Surgery: In a discrete choice experiment study comparing pharmacological and surgical options in 293 patients with UC, Bewtra *et al* observed that patients were willing to accept high levels of serious adverse risk from medical therapy to avoid an ostomy.[141] They also observed that in case durable clinical remission could not be achieved with medications, patients were willing to accept a ileo-anal pouch anastomosis surgery, valuing it to be equivalent to persistent mild disease activity. In another questionnaire study of patients with UC, gastroenterologists and colorectal surgeons, Bryne and colleagues observed that patient preferences are more closely aligned to those of gastroenterologists rather than colorectal surgeons.[142] For example, at time of active disease, 89% of patients, 69% of gastroenterologists and 55% of surgeons were willing to trade part of their life expectancy to avoid a permanent stoma.

We did not identify any study eliciting values and preferences of patients hospitalized with ASUC.

Cost-effectiveness

Though several cost-effectiveness analyses have been performed, they have shown conflicting findings due in part to diverse healthcare systems globally.[143, 144] In most analyses, colectomy dominated medical management, but as reported above, is inconsistent with patients' values and preferences. Studies have variably demonstrated that TNF-α antagonists and vedolizumab may or may not be more cost-effective than conventional therapy for outpatients with moderate to severe UC. In patients hospitalized with corticosteroid-refractory ASUC, infliximab was deemed cost-effective when compared with cyclosporine or surgery.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

While several significant advancements have been made in the treatment of patients with moderate to severe UC and ASUC, this technical review identified some key knowledge gaps which merit further evaluation to inform clinical guidelines and practice.

1. Personalization and positioning of therapies: With increasing availability of different biologics and targeted immunosuppressive therapies for treating outpatients with moderate-severe UC, there is clearly a need for identifying biomarkers predictive of response to individual therapies, to facilitate optimal choice of therapies. While awaiting biomarkers, validated clinical prediction models may be helpful, if sufficiently discriminatory to help identify patients who have a low vs. high probability of response to specific therapies. Ongoing research efforts using multi-omic platforms using serum, stool and tissue specimens have potential to inform biomarkers predictive of response to specific therapies. Once these are available, clinical trials or prospective comparative effectiveness studies using integrated clinical-, pharmacokinetic- and biomarker-

based treatment positioning strategies vs. usual care could provide guidance on appropriate management strategies.

2. Novel combinations of available therapies: It makes intuitive sense that a combination of biological drugs with different mechanisms of action may be more effective than any agent uses alone. However, there has been limited assessment of role of combination therapy with different biologic agents in patients with moderate to severe UC, with the only completed clinical trial, being terminated early, and unable to adequately inform role of combination therapy for maintenance of remission.

3. Shared decision-making in management of moderate-severe UC and ASUC: As noted in the review, different therapies have distinctive risk-benefit profiles, with varying balance of treatment efficacy vs. risk of treatment-related side effects. In addition, different patients based on age, clinical phenotype and disease status, have different risks of disease- vs. treatment-related complications. Accurate and validated risk prediction models to accurately identify patients at high risk of disease- vs. treatment-related complications, and how different treatments modify these risks, is vital to know and communicate effectively to patients. Pairing this information with patients' values and preferences would facilitate shared decision-making, as the treatment landscape rapidly evolves in this field.

4. Treatment targets in UC: Treatment targets with UC are in evolution. It is unclear how well targeting an integrated clinical and biomarker remission (for example, symptoms combined with calprotectin) compares to endoscopic remission. Likewise, the anticipated magnitude of benefit in downstream consequences (decreasing colectomy, healthcare utilization) vs. risks and costs, with treating to different treatment targets – conventional endoscopic remission (Mayo endoscopy subscore 0/1) vs. deeper remission (Mayo endoscopy subscore 0) vs. histologic remission. Different therapies have different rates of achieving different targets, often incrementally difficult from clinical and biochemical, to endoscopic, to histologic remission, and may result different intensity of therapies with associated risks and costs.

5. Inpatient management of corticosteroid-refractory patients with ASUC: As noted above, there are limited medical options for inpatient management of corticosteroid-refractory patients with ASUC, currently limited to infliximab and calcineurin inhibitors. Other therapies merit evaluation. Similarly, prospective evaluation of routine vs. selective use of intensive infliximab dosing regimens in these patients is warranted. When selectively used, well-defined and validated dosing calculators accurately estimating drug utilization would be helpful, to allow flexible dosing to ensure adequate infliximab concentrations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Focused clinical questions on the pharmacological management of moderate to severe ulcerative colitis, and corresponding questions in PICO format addressed in this technical review

S#	Focused Question	PICO Question			
		Patients	**Intervention**	**Comparator**	**Critical Outcomes**
OUTPATIENTS with MODERATE TO SEVERE UC					
1.	In adult outpatients with moderate to severe UC, what is the overall efficacy of TNF-α antagonists (infliximab, adalimumab, golimumab), vedolizumab, tofacitinib and ustekinumab for induction and maintenance of remission?	Adult outpatients with moderate to severe UC	• TNF-α antagonists (infliximab, adalimumab, golimumab) • Vedolizumab • Tofacitinib • Ustekinumab	Placebo	• Induction of remission • Maintenance of remission
2.	In adult outpatients with moderate to severe UC, what is the comparative efficacy of different biologic agents (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) and tofacitinib, in biologic-naïve and in patients with prior TNF-α antagonist exposure, for induction and maintenance of remission?	Adult outpatients with moderate to severe UC, (A) biologic-naïve and (B) prior exposure to TNF-α antagonist	• Infliximab • Adalimumab • Golimumab • Vedolizumab • Tofacitinib • Ustekinumab	Placebo or another active comparator	• Induction of remission • Maintenance of remission
3.	In adult outpatients with moderate to severe UC, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?	Adult outpatients with moderate to severe UC	• Thiopurines (azathioprine, mercaptopurine) • Methotrexate (oral or subcutaneous)	Placebo (or 5-aminosalicylates)	• Achieving remission • Prevention of relapse (≈maintenance of remission)
4.	In adult outpatients with moderate to severe UC, is biologic monotherapy (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) or tofacitinib superior to immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?	Adult outpatients with moderate to severe UC	Monotherapy with • TNF-α antagonists (infliximab, adalimumab, golimumab) • Vedolizumab • Ustekinumab • Tofacitinib	Immunomodulators (thiopurines or methotrexate)	• Induction of remission • Maintenance of remission
5.	In adult outpatients with moderate to severe UC, is combination therapy of a	Adult outpatients with moderate to severe UC	Combination therapy with of a biologic agent (infliximab, adalimumab,	• Biologic monotherapy (infliximab,	• Induction of remission

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S#	Focused Question	PICO Question			
		Patients	**Intervention**	**Comparator**	**Critical Outcomes**
	biologic agent (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) with an immunomodulator (thiopurines or methotrexate) superior to biologic monotherapy or immunomodulator monotherapy for induction and maintenance of remission?		golimumab, vedolizumab, ustekinumab) + immunomodulator (thiopurines or methotrexate)	• adalimumab, golimumab, vedolizumab, ustekiumab) • Immunomodulator monotherapy (thiopurines or methotrexate)	• Maintenance of remission
6.	In adult outpatients with moderate to severe ulcerative colitis, is top-down therapy superior to step therapy for induction and maintenance of remission?	Adult outpatients with moderate to severe UC	Top-down therapy • Upfront use of biologics and/or immunomodulator therapy • Upfront use of biologic-based combination therapy	Step therapy • Acceleration to biologic and/or immunomodulator therapy only after failure of 5-aminosalicylates • Initial use of immunomodulator or biologic monotherapy	• Induction of remission • Maintenance of remission
7.	In adult outpatients with moderate to severe UC with prior failure of 5-aminosalicylates, currently being treated with immunomodulators, biologic therapy or tofacitinib, is continuing 5-aminosalicylates superior to stopping 5-aminosalicylates for inducing and maintaining remission?	Adult outpatients with moderate to severe UC with prior failure of 5-ASA, currently being treated with immunomodulators or biologic therapy	Continuation of 5-ASA	Stopping 5-ASA	• Induction of remission • Maintenance of remission
HOSPITALIZED patients with ACUTE SEVERE ULCERATIVE COLITIS					
8.	In hospitalized patients with acute severe ulcerative colitis, what is the optimal dose of intravenous methylprednisolone for decreasing risk of colectomy?	Adults hospitalized with acute severe ulcerative colitis	Intravenous methylprednisolone equivalent of 40–60mg/d	Intravenous methylprednisolone equivalent of >60mg/d	Short-term colectomy (within 3 months of hospitalization)
9.	In hospitalized patients with acute severe ulcerative colitis, without gastrointestinal infection, is adjunctive antibiotic therapy more effective than no antibiotic therapy for decreasing risk of colectomy?	Adults hospitalized with acute severe ulcerative colitis being treated with intravenous corticosteroids	Antibiotics	Placebo or no antibiotics	Short-term colectomy
10.	In hospitalized patients with acute severe ulcerative colitis, refractory to intravenous corticosteroids, what is the overall efficacy of TNF-α antagonists (infliximab, adalimumab, golimumab), vedolizumab, tofacitinib,	Adults hospitalized with acute severe ulcerative colitis, refractory to intravenous corticosteroids	• TNF-α antagonists (infliximab, adalimumab, golimumab) • Vedolizumab	Placebo	Short-term colectomy

S#	Focused Question	PICO Question			
		Patients	**Intervention**	**Comparator**	**Critical Outcomes**
	immunomodulators, cyclosporine and tacrolimus for decreasing risk of colectomy?		• Tofacitinib • Immunomodulators (thiopurines, methotrexate) • Calcineurin inhibitors (cyclosporine, tacrolimus)		
11.	In hospitalized patients with acute severe ulcerative colitis, refractory to intravenous corticosteroids, is infliximab superior to cyclosporine for decreasing risk of colectomy?	Adults hospitalized with acute severe ulcerative colitis, refractory to intravenous corticosteroids	Infliximab	Intravenous cyclosporine	Short-term colectomy
12.	In hospitalized patients with acute severe ulcerative colitis being treated with infliximab, is routine administration of intensive dosing regimens superior to standard dosing regimens in decreasing risk of colectomy?	Adults hospitalized with acute severe ulcerative colitis, refractory to intravenous corticosteroids, being treated with infliximab	Intensive infliximab dosing regimen (shortened interval between infliximab doses or dose stacking and/or induction with higher dose infliximab)	Standard infliximab induction regimen	Short-term colectomy

Table 2.

GRADE Evidence Profile comparing infliximab, adalimumab, golimumab, vedolizumab and tofacitinib with placebo for induction and maintenance of remission in patients with moderate to severe ulcerative colitis. Note, for tofacitinib, both doses 5mg twice/day and 10mg twice/day were combined for maintenance of remission outcome

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with infliximab				
Induction of clinical remission (CRITICAL)	45/354 (12.7%)	**130/356 (36.5%)**	**RR 2.85** (2.11 to 3.86)	185 more per 1,000 (from 111 more to 286 more)	710 (5 RCTs)	⊕⊕⊕◯ [1] MODERATE
Maintenance of clinical remission (CRITICAL)	48/334 (14.4%)	108/333 (32.4%)	**RR 2.25** (1.67 to 3.05)	188 more per 1,000 (from 100 more to 307 more)	667 (4 RCTs)	⊕⊕⊕◯ [1] MODERATE
ADALIMUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with placebo	**Risk with infliximab**				
Induction of clinical remission (CRITICAL)	46/472 (9.7%)	**74/468 (15.8%)**	**RR 1.62** (1.15 to 2.29)	62 more per 1,000 (from 15 more to 129 more)	940 (3 RCTs)	⊕⊕⊕◯ [1] MODERATE
Maintenance of clinical remission (CRITICAL)	29/342 (8.5%)	**84/425 (19.8%)**	**RR 2.28** (1.52 to 3.42)	192 more per 1,000 (from 78 more to 363 more)	767 (2 RCTs)	⊕⊕⊕◯ [1] MODERATE
GOLIMUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with placebo	**Risk with infliximab**				
Induction of clinical remission (CRITICAL)	23/320 (7.2%)	**58/324 (17.9%)**	**RR 2.49** (1.58 to 3.93)	149 more per 1,000 (from 58 more to 239 more)	644 (2 RCTs)	⊕⊕⊕◯ [1] MODERATE
Maintenance of clinical remission (CRITICAL)	36/185 (19.5%)	**67/183 (36.6%)**	**RR 1.88** (1.32 to 2.68)	132 more per 1,000 (from 48 more to 252 more)	368 (2 RCTs)	⊕⊕⊕◯ [1,2] MODERATE
VEDOLIZUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with placebo	**Risk with infliximab**				
Induction of clinical remission (CRITICAL)	18/231 (7.8%)	**68/393 (17.3%)**	**RR 2.22** (1.36 to 3.64)	122 more per 1,000 (from 36 more to 264 more)	624 (2 RCTs)	⊕⊕⊕◯ [1] MODERATE
Maintenance of clinical remission (CRITICAL)	33/168 (19.6%)	**74/163 (45.4%)**	**RR 2.31** (1.63 to 3.28)	197 more per 1,000 (from 94 more to 342 more)	331 (2 RCTs)	⊕⊕⊕◯ [1] MODERATE
TOFACITINIB COMPARED TO PLACEBO FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**

	Risk with placebo	Risk with infliximab				
Induction of clinical remission (CRITICAL)	19/282 (6.7%)	**176/938 (18.8%)**	**RR 3.22** (2.03 to 5.08)	222 more per 1,000 (from 103 more to 408 more)	1220 (3 RCTs)	⊕⊕⊕◯ [1] MODERATE
Maintenance of clinical remission (CRITICAL)	22/198 (11.1%)	**149/395 (37.7%)**	**RR 3.09** (1.99 to 4.79)	203 more per 1,000 (from 110 more to 308 more)	593 (1 RCT)	⊕⊕⊕◯ [1] MODERATE

USTEKINUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERE ULCERATIVE COLITIS

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with infliximab				
Induction of clinical remission (CRITICAL)	17/319 (5.3%)	**50/322 (15.5%)**	**RR 2.91** (1.72 to 4.94)	191 more per 1,000 (from 72 more to 394 more)	641 (1 RCTs)	⊕⊕⊕◯ [1] MODERATE
Maintenance of clinical remission (CRITICAL)	42/175 (24.0%)	**77/176 (43.8%)**	**RR 1.83** (1.33 to 2.49)	125 more per 1,000 (from 50 more to 224 more)	351 (1 RCT)	⊕⊕⊕◯ [1] MODERATE

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for imprecision since optimal information size not met (<200 events)

[2] Though statistical heterogeneity was noted, with use of fixed effects meta-analysis, estimate was largely driven by larger, high quality trials

Table 3.

GRADE Summary of Findings reporting the comparative efficacy of different pharmacological agents for inducing clinical remission and endoscopic remission in biologic-naïve patients with moderate to severe ulcerative colitis

	Relative effect (Odds ratio, 95% CI)		Overall Quality of Evidence
	Clinical Remission	**Endoscopic Remission**	
Selected agents vs. Adalimumab			
Infliximab	**2.10 (1.16–3.79)**	**2.10 (1.35–3.25)**	**Moderate (imprecision)**
Golimumab	1.44 (0.76–2.75)	1.10 (0.71–1.71)	Low (very serious imprecision)
Vedolizumab *	**1.62 (1.14–2.31)** *	**1.81 (1.29–2.53)** *	Moderate (imprecision)
Tofacitinib	1.10 (0.51–2.34)	1.28 (0.72–2.29)	Very low (very serious imprecision, intransitivity)
Ustekinumab	1.05 (0.48–2.32)	1.17 (0.65–2.13)	Low (very serious imprecision)
Selected agents vs. Golimumab			
Infliximab	1.46 (0.73–2.90)	**1.91 (1.20–3.03)**	Low (very serious imprecision)
Vedolizumab	0.91 (0.44–1.86)	1.45 (0.80–2.61)	Low (very serious imprecision)
Tofacitinib	0.76 (0.33–1.76)	1.17 (0.64–2.12)	Very low (very serious imprecision, intransitivity)
Ustekinumab	0.73 (0.31–1.74)	1.07 (0.58–1.98)	Low (very serious imprecision)
Selected agents vs. Vedolizumab			
Infliximab	1.60 (0.87–2.97)	1.32 (0.73–2.37)	Low (very serious imprecision)
Tofacitinib	0.84 (0.39–1.82)	0.80 (0.40–1.62)	Very low (very serious imprecision, intransitivity)
Ustekinumab	0.80 (0.35–1.83)	0.74 (0.36–1.51)	Low (very serious imprecision)
Selected agents vs. Tofacitinib			
Infliximab	1.91 (0.83–4.38)	1.64 (0.90–2.97)	Very low (very serious imprecision, intransitivity)
Ustekinumab	0.96 (0.38–2.45)	0.92 (0.45–1.89)	Very low (very serious imprecision, intransitivity)
Selected agents vs. Ustekinumab			
Infliximab	2.00 (0.89–4.46)	1.78 (0.97–3.29)	Low (very serious imprecision)

* (Evidence derived from direct comparison in VARSITY trial for outcome of achieving remission at week 52, not from network meta-analysis, focusing on biologic naïve patients)

Table 4.

GRADE Summary of Findings reporting the comparative efficacy of different pharmacological agents for inducing clinical remission and endoscopic remission in TNFα antagonist-exposed patients with moderate to severe ulcerative colitis

	Relative effect (Odds ratio, 95% CI)		Overall Quality of Evidence
	Clinical Remission	**Endoscopic Remission**	
Selected agents vs. Adalimumab			
Vedolizumab *	1.33 (0.59–2.98) *	1.36 (0.66–2.83) *	Low (very serious imprecision)
Tofacitinib	**11.05 (1.79–68.41)**	**4.29 (1.63–11.33)**	Low (imprecision, intransitivity)
Ustekinumab	**10.71 (2.01–57.20)**	**3.32 (1.29–8.58)**	Low (imprecision, intransitivity)
Selected agents vs. Vedolizumab			
Tofacitinib	**6.18 (1.00–38.00)**	**3.85 (1.51–9.80)**	Low (imprecision, intransitivity)
Ustekinumab	**5.99 (1.13–31.76)**	**2.98 (1.20–7.41)**	Low (imprecision, intransitivity)
Selected agents vs. Tofacitinib			
Ustekinumab	0.97 (0.11–8.72)	0.77 (0.28–2.18)	Very low (very serious imprecision, intransitivity)

* (Evidence derived from direct comparison in VARSITY trial for outcome of achieving remission at week 52, not from network meta-analysis, focusing on patients with prior exposure to **TNF-α antagonists**

Table 5.

GRADE Summary of Findings reporting the comparative efficacy of different pharmacological agents for maintaining clinical remission and endoscopic remission in anti-TNF-exposed patients with moderate to severe ulcerative colitis

	Relative effect (Odds ratio, 95% CI)		Overall Quality of Evidence
	Clinical Remission	Endoscopic Remission	
Selected agents vs. Adalimumab			
Infliximab	1.17 (0.62–2.20)	1.31 (0.75–2.28)	Very low quality (very serious imprecision, intransitivity)
Vedolizumab	N/A	N/A	N/A
Selected agents vs. Vedolizumab			
Infliximab	0.72 (0.35–1.49)	0.73 (0.37–1.42)	Very low quality (very serious imprecision, intransitivity)

	Relative effect (Odds ratio, 95% CI)		Overall Quality of Evidence
	Clinical Remission	Endoscopic Remission	
Selected agents vs. Golimumab			
Vedolizumab	0.88 (0.16–5.01)	1.38 (0.38–5.05)	Very low quality (very serious imprecision, intransitivity)
Tofacitinib 5mg BID	1.03 (0.15–7.27)	1.25 (0.30–5.16)	Very low quality (very serious imprecision, intransitivity)
Ustekinumab	0.61 (0.09–4.20)	0.83 (0.20–3.35)	
Selected agents vs. Vedolizumab			
Tofacitinib 5mg BID	1.17 (0.20–6.90)	0.90 (0.24–3.42)	Very low quality (very serious imprecision, intransitivity)
Ustekinumab	0.69 (0.12–3.98)	0.60 (0.16–2.22)	Very low quality (very serious imprecision, intransitivity)
Selected agents vs. Tofacitinib			
Ustekinumab	0.59 (0.08–4.28)	0.66 (0.15–2.85)	Very low quality (very serious imprecision, intransitivity)

*Treat straight-through trials

*Re-randomization of responders

Table 6.

GRADE Evidence Profile comparing thiopurines vs. no thiopurines for achieving steroid-free remission, and preventing relapse in patients with steroid-dependent moderate to severe ulcerative colitis

Thiopurines COMPARED TO No Thiopurines FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk without Thiopurines	**Risk with Thiopurines**				
Achieving clinical remission (CRITICAL)	54/97 (55.7%)	**72/105 (68.6%)**	**RR 1.25** (1.01 to 1.56)	139 more per 1,000 (from 6 more to 213 more)	203 (5 RCTs)	⨁◯◯◯ *1,2,3* VERY LOW
Relapse after achieving remission (CRITICAL)	90/146 (61.6%)	**59/157 (37.6%)**	**RR 0.61** (0.49 to 0.77)	240 fewer per 1,000 (from 314 fewer to 142 more)	303 (7 RCTs)	⨁⨁◯◯ *1,3* LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Rated down for risk of bias (inadequate blinding)

2 Rated down for indirectness (not truly induction of remission, since majority of patients received corticosteroids for inducing remission; outcomes in 1/5 trials not standardized)

3 Rated down for imprecision due to low event rate

Table 7.

GRADE Evidence Profile comparing methotrexate vs. no methotrexate for achieving steroid-free remission, and preventing relapse in patients with steroid-dependent moderate to severe ulcerative colitis

Methotrexate COMPARED TO No Methotrexate FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk without methotrexate	**Risk with methotrexate**				
Achieving clinical remission (CRITICAL)	30/96 (31.3%)	**40/102 (39.2%)**	**RR 1.31** (0.89 to 1.94)	97 more per 1,000 (from 34 fewer to 294 more)	198 (3 RCTs)	⨁◯◯◯ [1,2] VERY LOW
Relapse after achieving remission (CRITICAL)	39/60 (65.0%)	**44/65 (67.7%)**	**RR 1.01** (0.79 to 1.29)	7 more per 1,000 (from 136 fewer to 189 more)	125 (3 RCTs)	⨁◯◯◯ [1,2] VERY LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for indirectness (different modes of administering MTX, majority of patients received corticosteroids for inducing remission)

[2] Rated down for very serious imprecision with very wide CIs

Table 8.

GRADE Evidence Profile comparing biologic monotherapy (or tofacitinib) vs. immunomodulator monotherapy for achieving remission in patients with moderate to severe ulcerative colitis. Note, no trials of maintenance therapy were comparing biologic monotherapy (or tofacitinib) vs. immunomodulator monotherapy were identified

BIOLOGIC MONOTHERAPY OR TOFACITINIB COMPARED TO IMMUNOMODULATOR MONOTHERAPY FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with immunomodulator	**Risk with Biologic therapy**				
Achieving clinical remission (CRITICAL)	18/79 (22.8%)	**17/78 (21.8%)**	**RR 0.96** (0.53 to 1.72)	9 fewer per 1,000 (from 107 fewer to 164 more)	157 (1 RCT)	⨁◯◯◯ *1,2,3*

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Rated down for risk of bias

2 Rated down for indirectness (discrepant findings based on direct and indirect evidence, direct evidence being available only for comparison of infliximab vs. azathioprine, but no other biologic agent or tofacitinib)

3 Rated down for very serious imprecision

Table 9.

GRADE Evidence Profile comparing TNF-α antagonists + immunomodulators vs. TNF-α antagonist monotherapy for achieving steroid-free remission in patients with moderate to severe ulcerative colitis. Note, the trial included infliximab and azathioprine as interventions. No trial of maintenance therapy comparing TNF-α antagonists + immunomodulators vs. TNF-α antagonist monotherapy was identified.

COMBINATION THERAPY WITH TNF-α ANTAGONISTS + IMMUNOMODULATORS COMPARED TO TNF-α ANTAGONIST MONOTHERAPY FOR MODERATE TO SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with TNF-α antagonist monotherapy	**Risk with combination therapy**				
Achieving clinical remission (CRITICAL)	17/78 (21.8%)	**31/80 (38.8%)**	**RR 1.78** (1.08 to 2.94)	170 more per 1,000 (from 17 more to 423 more)	158 (1 RCT)	⊕⊕⊕◯ [1] MODERATE

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for imprecision since optimal information size not met (<200 events)

Table 10.

GRADE Evidence Profile comparing biologic agents + immunomodulators vs. immunomodulator monotherapy for achieving steroid-free remission in patients with moderate to severe ulcerative colitis. Note, the trial included infliximab and azathioprine as interventions. No trial of maintenance therapy comparing biologic agents + immunomodulators vs. immunomodulator monotherapy was identified.

COMBINATION THERAPY WITH BIOLOGIC AGENTS + IMMUNOMODULATORS COMPARED TO IMMUNOMODULATOR MONOTHERAPY FOR MODERATE-SEVERE ULCERATIVE COLITIS						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with Immunomodulator	**Risk with Combination Therapy**				
Achieving clinical remission (CRITICAL)	18/79 (22.8%)	**31/80 (38.8%)**	**RR 1.70** (1.04 to 2.78)	159 more per 1,000 (from 9 more to 406 more)	159 (1 RCT)	⨁⨁⨁◯ [1] MODERATE

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for imprecision since optimal information size not met (<200 events)

Table 11.

GRADE Evidence Profile comparing continuing vs. stopping 5-aminosalicylates in biologic- and/or immunomodulator-treated patients with moderate to severe ulcerative colitis who have failed 5-aminosalicylates.

CONTINUING 5-AMINOSALICYLATE COMPARED TO STOPPING 5-AMINOSALICYLATE in biologic- and/or immunomodulator-treated patients with MODERATE TO SEVERE ULCERATIVE COLITIS who have FAILED 5-ASA						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk without 5-ASA	**Risk with concomitant 5-ASA**				
Induction of clinical remission (CRITICAL)	68/273 (24.9%)	234/1035 (22.6%)	**RR 0.94** (0.74 to 1.18)	15 fewer per 1,000 (from 65 fewer to 45 more)	1308 (5 RCTs)	⨁⨁◯◯ [1,2] LOW
Maintenance of clinical remission (CRITICAL)	97/203 (47.8%)	**308/721 (42.7%)**	**RR 0.92** (0.78 to 1.09)	38 fewer per 1,000 (from 105 fewer to 43 more)	924 (4 RCTs)	⨁⨁◯◯ [1,2] LOW
GRADE Working Group grades of evidence **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

[1] Rated down for indirectness (not trials of continuing vs. stopping 5-ASA, but rather concomitant 5-ASA vs. no concomitant 5-ASA at trial entry)

[2] Rated down for serious imprecision with wide CIs

Table 12.

GRADE Evidence Profile comparing antibiotics vs. placebo in hospitalized patients with acute severe ulcerative colitis, without gastrointestinal infection.

Adjuvant Antibiotic Therapy Compared to Placebo for Hospitalized Patients with acute severe ulcerative colitis, without gastrointestinal infection						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with Placebo	**Risk with Antibiotics**				
Short-term colectomy	26/81 (32.1%)	**20/85 (23.5%)**	**RR 0.79** (0.46 to 1.35)	67 fewer per 1,000 (from 173 fewer to 112 more)	166 (4 RCTs)	⨁◯◯◯ *1,2,3* VERY LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Rated down for risk of bias (random sequence generation, allocation concealment, unclear risk of bias in blinding of outcome assessors/analysts)

2 Rated down for very serious imprecision

3 Rated down for inconsistency (in intervention – different antibiotics used)

Table 13.

GRADE Evidence Profile comparing infliximab and cyclosporine vs. placebo for decreasing short-term risk of colectomy, in patients hospitalized with corticosteroid-refractory acute severe ulcerative colitis

Infliximab compared to Placebo for Hospitalized Patients with Acute Severe Ulcerative Colitis, refractory to intravenous corticosteroids						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with Placebo	**Risk with Infliximab**				
Short-term colectomy	14/21 (66.7%)	**7/24 (29.2%)**	**RR 0.44** (0.22 to 0.87)	373 fewer per 1,000 (from 520 fewer to 87 fewer)	45 (1 RCTs)	⨁⨁⨁◯ [1] MODERATE
Cyclosporine compared to Placebo for Hospitalized Patients with Acute Severe Ulcerative Colitis, refractory to intravenous corticosteroids						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with Placebo	**Risk with Cyclosporine**				
Short-term colectomy	4/9 (44.4%)	**3/11 (27.3%)**	**RR 0.61** (0.18 to 2.01)	173 fewer per 1,000 (from 364 fewer to 471 more)	20 (1 RCTs)	⨁⨁◯◯ [1] LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for imprecision due to low number of events

[2] Rated down for very serious imprecision (very wide confidence intervals)

Table 14.

GRADE Evidence Profile comparing infliximab vs. cyclosporine for decreasing short-term risk of colectomy, in patients hospitalized with corticosteroid-refractory acute severe ulcerative colitis

Infliximab compared to Cyclosporine for Hospitalized Patients with Acute Severe Ulcerative Colitis, refractory to intravenous corticosteroids						
Outcomes	**Study event rates (95% CI)**		**Relative effect (95% CI)**	**Absolute effect***	**No of participants (studies)**	**Quality of the evidence (GRADE)**
	Risk with Cyclosporine	**Risk with Infliximab**				
Short-term colectomy	51/193 (26.4%)	**51/192 (26.6%)**	**RR 1.00** (0.72 to 1.40)	0 fewer per 1,000 (from 74 fewer to 106 more)	285 (2 RCTs)	⨁⨁◯◯ [1,2] LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for risk of bias (open-label)

[2] Rated down for serious imprecision