Comparative Efficacy and Tolerability of Pharmacological Agents for Management of Mild to Moderate Ulcerative Colitis: A Network Meta-analysis

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Abstract

Background: We performed a systematic review with network meta-analysis to inform the comparative efficacy and tolerability of different therapies in the management of patients with left-sided or extensive mild to moderately active ulcerative colitis (UC).

Methods: Through a systematic review up to March 1, 2018, we identified randomized controlled trials (RCTs) in (a) adults with left-sided or extensive mild-moderate UC, (b) treated with oral sulfasalazine, diazo-bonded 5-aminosalicylates (5-ASA), mesalamine (low- [<2 g/d], standard- [2–3 g/day] or high-dose [>3 g/day]), controlled ileal-release budesonide or budesonide MMX, alone or in combination with rectal 5-ASA therapy, and (c) compared to each other or placebo for (d) induction or maintenance of clinical remission. We performed pairwise and random-effects network meta-analysis using frequentist approach, and calculated odds ratio (OR) and 95% confidence intervals (CI); agents were ranked using surface under the cumulative ranking (SUCRA) probabilities. We used GRADE criteria to appraise quality of evidence.

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Findings: Based on 48 induction RCTs (8020 participants), combined oral and rectal 5-ASA (SUCRA, 0·99) and high-dose mesalamine (>3g/d) (SUCRA, 0·82) were ranked highest for induction of remission; both of these interventions were superior to standard-dose mesalamine (2–3g/d) (failure to induce remission with combined oral and rectal 5-ASA: OR, 0·41; 95% CI, 0·22–0·77; high-dose mesalamine: OR, 0·78; 95% CI, 0·66–0·93) with moderate confidence in estimates. Based on 28 maintenance RCTs (4218 participants), all interventions were superior to placebo for maintenance of remission; however, neither combined oral and rectal 5-ASA, nor high-dose mesalamine were superior to standard-dose mesalamine.

Interpretation: In patients with mild-moderate extensive UC, combined oral and topical mesalamine therapy and high-dose mesalamine are superior to standard-dose mesalamine for induction of remission, but not maintenance of remission. Standard-dose mesalamine may be the preferred agent for maintenance in most patients.

INTRODUCTION

Ulcerative colitis (UC) is a chronic disabling inflammatory bowel disease that generally begins in young adulthood and lasts throughout life. Although the incidence and prevalence of UC has stabilized in Western Europe and North America (affecting >0.3% of the population), its incidence continues to rise in newly industrialized countries.[1] Based on longitudinal population-based cohort studies, less than 20% of patients experience an aggressive disease course and the majority of patients with UC have a mild-moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity.[2–8] More than >90%patients receive 5-aminosalicylates (5-ASA) within 1 year of diagnosis for management of UC, and on long-term follow-up, 60–87% patients continue 5-ASA use. Only 50% of patients receive corticosteroids during the course of their disease, with even lower rates of use of immunosuppressive (20%) and biologic therapy (5–10%).[2–8]

Despite the majority of patients with UC having mild-moderate disease activity, there is considerable practice variability, between IBD specialists, gastroenterologists and primary care physicians.[9] Some important area of variability include the dosing of mesalamine for induction and maintenance of remission, comparative efficacy of diazo-bonded 5-ASA and mesalamine, role of combined oral and topical 5-ASA, and positioning of recently approved budesonide MMX in the management of patients with extensive mild-moderate UC. Previous pair-wise meta-analyses focusing on head-to-head comparisons, while thorough and informative, have not adequately informed comparative efficacy of different approaches in the management of mild-moderate UC, due to paucity of head-to-head trials for some key comparisons (for example, role of high-dose 5-ASA (>3g/d) vs. standard-dose 5-ASA (2–3g/d, positioning of budesonide MMX, etc.).[10–12] In contrast, network meta-analyses, which combine direct evidence (from head-to-head trials) and indirect evidence (comparisons of different interventions against a common comparator) may better inform comparative efficacy of different treatment approaches.[13]

Hence, we conducted a systematic review with pairwise and network meta-analyses to compare the efficacy and tolerability of candidate agents (sulfasalazine, diazo-bonded 5-ASA including olsalazine and balsalazide, mesalamine (low- [<2 g/d], standard- [2–3 g/day] or high-dose [>3 g/day]), controlled ileal release budesonide, budesonide MMX, alone or in combination with rectal 5-ASA therapy) in patients with extensive or left-sided mild-moderate UC. We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for network meta-analysis to appraise quality of evidence.[14]

METHODS

We performed this systematic review according to the guidelines as prescribed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for systematic reviews incorporating network meta-analyses for health care interventions and also following an *a priori* established protocol (see appendix p2).[15] For our research protocol, we followed good research practices as outlined in the Internal Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analysis for health-care decision making.[16]

Data Sources and Searches

A medical librarian (LJP) designed and performed a comprehensive literature search with input from study investigators utilizing various databases (included Ovid Epub, Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science) from inception to December 2015; the search was subsequently updated on Medline on March 1, 2018. The search strategy contained no language restrictions and used controlled vocabulary supplemented with keywords, expanded terminology, and varying algorithms to search for RCTs in adults with mild-moderate UC. The references of all identified relevant studies, as well as recent Cochrane reviews on the topic, were also manually reviewed to identify any potential relevant studies. Two study reviewers (NHN, MF) independently reviewed each study to exclude non-relevant studies with discrepancies discussed and resolved by a third reviewer (SS). Details of the search strategy are reported in the online supplement (see appendix p8). Figure 1 shows the schematic diagram of study selection.

Study Selection

Randomized controlled trials (RCTs) were included if they met the following inclusion criteria: (a) Adults (age 17 years) with extensive or left-sided mild-moderate UC; (b) Interventions: sulfasalazine, diazo-bonded 5-ASA including olsalazine and balsalazide, mesalamine (low- [<2 g/d], standard- [2–3 g/day] or high-dose [>3 g/day]), controlled ileal release budesonide, budesonide MMX, alone or in combination with rectal 5-ASA therapy; (c) comparator: any other active intervention or placebo; and (d) outcomes included induction and/or maintenance of clinical remission with or without endoscopic remission. Minimum duration of therapy for trials of induction and maintenance therapy was 4 and 24 weeks, respectively. We assumed comparability of different commercial preparations of

mesalamine at equivalent doses based on an exhaustive systematic review that demonstrated that different mesalamine formulations have comparable efficacy and safety.[17]

We excluded the following studies: (a) observational studies, (b) short duration trials, (c) 5-ASA trials in patients with moderate-severe disease or steroid-dependent UC, trials in patients with proctitis, or trials of rectal therapy alone in patients with left-sided colitis and (d) trials of non-conventional agents which are not approved for UC.

Data Abstraction and Risk of Bias Assessment

Data abstraction was conducted with a standardized case report form to capture data on study-, participant- and treatment-related characteristics. Two reviewers independently reviewed and abstracted data with discrepancies resolved by consensus in consultation with a third reviewer. Risk of bias was assessed by two sets of authors independently, using the Cochrane Risk of Bias assessment tool, with disagreements addressed by re-evaluation, in conjunction with a third reviewer.[18]

Outcomes

Our primary outcome was overall and comparative efficacy of interventions reported as failure to achieve clinical remission in patients with active disease and failure to maintain clinical remission in patients with quiescent UC. Secondary outcomes of interest included failure to induce endoscopic remission (as defined by each study), and tolerability, defined as discontinuation of therapy due to adverse events.

Clinical remission was measured using various disease activity indices (DAI), most commonly, UCDAI, Mayo Clinic Score, simple clinical colitis activity index, Sutherland DAI, Rachmilewitz Clinical Activity Index, etc. These DAIs generally combined measures of stool frequency, rectal bleeding and/or physician global assessment, with a measure of endoscopic disease activity; in most indices, all patients who achieved clinical remission were also in endoscopic remission. There were differences in definition of remission across different DAIs; in some studies, 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.

When outcomes were reported at multiple time points, then a hierarchical approach was followed. For assessment of induction trials, data abstraction hierarchy was at 6 weeks, then 4 weeks, and 8 weeks. For maintenance trials, last primary time point of individual trials was used for data abstraction. Mesalamine dosing was grouped as low-dose (<2g/d), standard-dose (2–3 g/d) and high-dose (>3g/d). For other interventions, where available, standard FDA-approved doses were used; however, trials of alternative doses of diazo-bonded 5-ASA and sulfasalazine were also included. All patients were analyzed in the group they were randomized to; patients lost to follow-up were considered as treatment failures.

Data Synthesis and Statistical Analysis

Direct pairwise meta-analysis was performed using a random effects model to estimate pooled OR and 95% CI.[19] Since outcomes were reported as failure to achieve or maintain

remission, ORs<1 indicate superior efficacy. We assessed statistical heterogeneity using I^2 statistic, with values over 50% indicating substantial heterogeneity, and small study effect was assessed by examining funnel plot asymmetry, where >10 trials were available.[20] Direct comparisons were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark).

We conducted network meta-analysis using a multivariate random-effects meta-regression, using consistency model, as described by Ian White.[21] We used a frequentist approach and provided a point estimate from the network along with 95% CI from the frequency distribution of the estimate. Decision to use frequentist approach was made *a priori* based on the statistical expertise of our team; results of frequentist and Bayesian approach is expected to be very similar. Network consistency was evaluated by comparing the direct estimates to the indirect estimates for each comparison, using a node-splitting technique. All network meta-analyses were performed using Stata v.14 (College Station, TX).

We calculated the relative ranking of interventions for induction and maintenance of clinical remission as their surface under the cumulative ranking (SUCRA), which represents the percentage of efficacy achieved by an approach compared to an imaginary approach that is always the best without uncertainty (i.e. SUCRA=100%).[22] Higher SUCRA scores correspond to greater efficacy and superior tolerability. To demonstrate imprecision of ranking probabilities, we also estimated how each treatment would rank in 100 iterations.

Finally, we generated estimates of absolute event rates (or absolute risk) by calculating the estimated risk difference (RD, also known as absolute risk reduction) by combining the odds ratio (OR) for each intervention against placebo and the median placebo response rate across trials as the assumed control risk (ACR), by using the formula: Risk difference = (OR*ACR-ACR+ACR*ACR-OR*ACR*ACR)/(1-ACR+OR*ACR). The risk difference, which represents the difference between the event rates in the intervention and control group, was added back to the ACR to generate an estimate of the absolute risk for each intervention. 95% CI for the estimates were generated using the 95% CI of the odds ratios in the above calculations.

Quality of Evidence

The quality of evidence derived from the pairwise and network meta-analysis was judged using the GRADE framework. In this approach, direct evidence from RCTs starts at high quality and can be rated down based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and/or publication bias, to levels of moderate, low and very low quality. The rating of indirect estimates starts at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate but can be rated down further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodological characteristics). If direct and indirect estimates were similar (i.e., coherent), then the higher of their rating was assigned to the network meta-analysis estimates.

RESULTS

From a total of 1316 unique citations identified through our comprehensive search strategy, we included 48 RCTs (8020 participants, including 1380 placebo-treated patients) comparing 8 active interventions for induction of remission,[23–70] and 28 RCTs (4218 participants, including 575 placebo-treated patients) comparing 6 active interventions for maintenance of remission (see appendix p26).[23,71–97] The available direct comparisons and network of trials for induction and maintenance of clinical remission are shown in Figures 1A and B.

Characteristics and Risk of Bias of the Included Trials

Summary characteristics of all included RCTs in the network meta-analysis are reported in the online supplement (see appendix p12). Induction trials were 4–12 weeks long, and trials of maintenance therapy were 24 to 72 weeks long. Overall, median rate of failure to induce clinical and endoscopic remission in placebo-arms of trials 87% (range, 45–96%), and 69% (range, 53–100%), respectively. In trials of maintenance therapy, median (range) of failure to maintain clinical remission in placebo-arms of trials was 56% (range, 33–75%). Most trials included patients with both left-sided and extensive UC; however, efficacy of oral therapy in these patients was not consistently stratified by disease location. Overall, most studies were deemed to be at low-risk of bias, except early trials of sulfasalazine which had high risk of bias.

Primary Outcomes

Failure to Induce Clinical Remission

Pairwise meta-analysis: In placebo comparisons, low-, standard, and high-dose mesalamine, diazo-bonded 5-ASA, and budesonide MMX were all significantly superior to placebo (see appendix p27). No trials comparing sulfasalazine with placebo were identified in patients with mild-moderate UC. On active comparisons, standard- and high-dose mesalamine was superior to low-dose mesalamine for induction of clinical remission (see appendix p29). High-dose mesalamine was not significantly superior to standard-dose mesalamine (relative risk [RR] for failure to induce remission, 0·94; 95% CI, 0·88–1·01); however, on subgroup analysis only in patients with moderate UC (ASCEND II, ASCEND III, Hiwatashi et al),[38,39,60] or reporting outcomes stratified by baseline UC disease severity, [37,41,42] high-dose mesalamine was significantly superior to standard-dose mesalamine (6 trials, 1589 patients; RR, 0·92; 95% CI, 0·86–0·99). Sulfasalazine, but not standard-dose mesalamine was inferior to diazo-bonded 5-ASA for induction of clinical remission (see appendix p30); there was a trend towards superiority of balsalazide over standard-dose mesalamine (RR, 0·73; 95% CI, 0·52–1·02). There was no significant difference in efficacy of sulfasalazine and mesalamine (RR, 1·07 [0·91–1·26]) (see appendix p30); on restricting analyses to standard-dose mesalamine, there was trend favoring superiority of mesalamine over sulfasalazine (RR, 0·79; 95% CI, 0·58–1·06). Combined oral and rectal 5-ASA therapy was superior to oral 5-ASA alone (see appendix p30). Overall, for all pairwise comparisons, there was mild-moderate heterogeneity ($I^2 < 50\%$), except for comparison of high-dose mesalamine vs. placebo and mesalamine vs. diazo-bonded 5-ASA.

Network meta-analysis: On network meta-analysis, low-, standard, and high-dose mesalamine, diazo-bonded 5-ASA, combined oral and rectal 5-ASA and budesonide MMX were superior to placebo for induction of clinical remission, with the largest effect size being observed with combined oral and rectal 5-ASA; sulfasalazine and controlled ileal-release budesonide were not superior to placebo (Figure 2A). On active comparisons, combined oral and rectal 5-ASA was significantly superior to all other interventions, except budesonide MMX where the results were not statistically significant (OR, 0·49; 95% CI, 0·24–1·02) (Figure 3). High-dose mesalamine was significantly superior to low- and standard-dose mesalamine, sulfasalazine, controlled ileal-release budesonide, but not more effective than diazo-bonded 5-ASA (OR, 0·85; 95% CI, 0·63–1·13) and budesonide MMX (OR, 0·94; 95% CI, 0·62–1·42). Standard-dose mesalamine was superior to low-dose mesalamine, sulfasalazine and controlled ileal-release budesonide, but not more effective than diazo-bonded 5-ASA or budesonide MMX (Figure 2B).

On SUCRA analysis, combined oral and rectal 5-ASA (SUCRA, 0·99) was ranked highest followed by high-dose mesalamine (SUCRA, 0.82); corresponding imprecision in ranking probabilities is shown in online supplement (see appendix p25). With a median placebo remission rate of 13% across trials, approximately 62·5%, 32·8% and 25·6% patients treated with combined oral and rectal 5-ASA, high-dose mesalamine and standard-dose mesalamine, respectively, may be expected to achieve induction of clinical remission. GRADE quality of evidence from direct and network-meta-analysis is summarized in Table 1. Overall, at least moderate quality evidence supports oral and rectal 5-ASA and high-dose 5-ASA for induction of clinical remission over standard-dose mesalamine and placebo.

Failure to Maintain Clinical Remission

Pairwise meta-analysis: In placebo comparisons, low- and standard-dose mesalamine and sulfasalazine, but not diazo-bonded 5-ASA, were significantly superior to placebo (see appendix p31); no placebo-controlled trials of high-dose 5-ASA or combination therapy of oral and rectal 5-ASA were identified. Of note, budesonide formulations are not approved or indicated for maintenance of remission. On active comparisons, standard-dose mesalamine was superior to low-dose mesalamine, and was not inferior to high-dose mesalamine for maintenance of clinical remission (see appendix p32). Diazo-bonded 5-ASA was significantly superior to mesalamine for maintenance of remission, though trials only used low-dose mesalamine (see appendix p33). There was a trend suggesting higher efficacy of diazo-bonded 5-ASA as compared to sulfasalazine (see appendix p33); all trials used sulfasalazine 2g/day, and 5 trials compared it with olsalazine. Sulfasalazine was numerically but not statistically inferior to mesalamine for maintenance of remission (see appendix p33); in 5/6 trials, low-dose mesalamine was used (0·75–1·5g/d). Based on 2 trials, combined oral and rectal 5-ASA was superior to oral 5-ASA for maintenance of remission (see appendix p33). Overall, for all pairwise comparisons, there was mild-moderate heterogeneity ($I^2 < 50\%$), except for comparison of diazo-bonded 5-ASA vs. placebo and sulfasalazine vs. placebo.

Network meta-analysis: On network meta-analysis, low-, standard, and high-dose mesalamine, diazo-bonded 5-ASA, sulfasalazine and combined oral and rectal 5-ASA were

superior to placebo for maintenance of clinical remission. On active comparisons, high- and standard-dose mesalamine were significantly superior to low-dose mesalamine (Figure 4). No other intervention was superior to other approaches, without any significant differences between standard- and high-dose mesalamine and combined oral and rectal 5-ASA.

On SUCRA analysis, combined oral and rectal 5-ASA (SUCRA, 0·82) and high-dose mesalamine (SUCRA, 0·82) were ranked highest, followed by standard-dose mesalamine (SUCRA, 0·69); corresponding imprecision in ranking probabilities is shown in online supplement (see appendix p25). With a median placebo rate of clinical relapse of 56% across trials in patients with quiescent UC, approximately 14·6%, 16·2% and 18·5% patients treated with combined oral and rectal 5-ASA, high-dose mesalamine and standard-dose mesalamine, respectively, may relapse over the course of one year. GRADE quality of evidence is summarized in Table 1. Overall, high quality evidence supports standard-dose mesalamine over low-dose mesalamine or placebo for maintenance of clinical remission; only low quality evidence supported oral and rectal 5-ASA and high-dose mesalamine over standard-dose mesalamine for maintenance.

Secondary Outcomes

Failure to Induce Endoscopic Remission: On network meta-analysis, overall and comparative efficacy of different interventions for induction of endoscopic remission was similar to findings on clinical remission (see appendix p34). All interventions, except low-dose mesalamine and controlled ileal-release budesonide were superior to placebo for induction of remission. On SUCRA analysis, combined therapy with oral and rectal 5-ASA (SUCRA, 0·95) and high-dose mesalamine (SUCRA, 0·81) were ranked highest.

Tolerability: On network meta-analysis of trials of induction therapy, standard- (OR, 0·48; 95% CI, 0·34–0·69) and high-dose mesalamine (OR, 0·37; 95% CI, 0·25–0·53) and diazo-bonded 5-ASA (OR, 0·44; 95% CI, 0·27–0·71) were better tolerated than placebo (lower rates of treatment discontinuation). On active comparisons, standard- and high-dose mesalamine were better tolerated than budesonide MMX and sulfasalazine (Figure 3). There was no difference in the tolerability of diazo-bonded 5-ASA and mesalamine; diazo-bonded 5-ASA was better tolerated than sulfasalazine and budesonide MMX. On SUCRA analysis, standard- (SUCRA, 0·73) and high-dose mesalamine (SUCRA, 0·93) and diazo-bonded 5-ASA (SUCRA, 0·81) were best tolerated, whereas sulfasalazine (SUCRA, 0·15) and budesonide MMX (SUCRA, 0·33) were not well tolerated.

In contrast, in trials of maintenance therapy, all agents were well tolerated in patients with quiescent disease; in fact, all doses of mesalamine and diazo-bonded 5-ASA were better tolerated than placebo (Figure 4). Sulfasalazine was also numerically better tolerated than placebo (OR, 0·45; 95% CI, 0·20–1·02).

Small study effects and network coherence—Formal assessment of funnel plot asymmetry was performed for one comparison (high-dose mesalamine vs. standard-dose mesalamine for failure to induce clinical remission) with >10 trials (see appendix p35); for other direct comparisons, funnel plot asymmetry assessment is not recommended. There was no evidence of network incoherence in trials of induction therapy. However, in trials of

maintenance therapy, network incoherence was observed for the comparison of low-dose mesalamine and sulfasalazine (p=0·003), diazo-bonded 5-ASA (p=0·04) and combination therapy of oral and rectal 5-ASA (p=0·007), and for the comparison of standard-dose mesalamine and combined therapy with oral and rectal 5-ASA (p=0·007).

DISCUSSION

The majority of patients with UC have mild-moderate disease activity and are at low risk of colectomy. These patients are frequently managed by primary care physicians and general gastroenterologists, with considerable practice variability.[9] Optimal management of these may reduce the risk of disease progression and complications. Through a systematic review with network meta-analysis, including 48 RCTs (8020 participants) comparing 8 active interventions for induction of remission, and 28 RCTs (4218 participants, including 575 placebo-treated patients) comparing 6 active interventions for maintenance of remission in patients with left-sided or extensive UC, we are able to inform the treatment approach in these patients. For induction of remission, combined oral and rectal 5-ASA is the most effective treatment strategy, followed by high-dose mesalamine (moderate confidence in estimates); standard-dose mesalamine is comparable to diazo-bonded 5-ASA, but superior to sulfasalazine. For maintenance of remission, standard- and high-dose mesalamine are comparable (low confidence in estimates), and superior to low-dose mesalamine (high confidence in estimates). Budesonide MMX is not more effective than combined oral and rectal 5-ASA or high-dose mesalamine and has inferior tolerability. Due to paucity of data stratified by disease location (extensive colitis vs. left-sided colitis) and use of rectal therapy alone as an effective treatment strategy for left-sided colitis, but not extensive colitis, we opted not to evaluate extensive and left-sided colitis separately.

Optimization of 5-ASA is often an under-utilized approach when managing patients with mild-moderate UC;[9] at the same time, there is occasional over-reliance of 5-ASA-based therapy with failure to recognize patients who may be at high-risk of colectomy, who may benefit from early escalation to immunosuppressive therapy. By informing comparative efficacy of different 5-ASA-based treatment strategies and a quantitative assessment of success of these therapies, we believe our findings can inform clinical practice and treatment guidelines.

Our study builds on findings from primary RCTs and prior meta-analyses, by systematically synthesizing available direct and indirect evidence on the efficacy and tolerability of treatment for the treatment of mild to moderately active extensive UC, and adding recent studies on budesonide MMX.[10–12] In clinical practice in patients with extensive UC, addition of rectal 5-ASA for induction of remission is frequently under-utilized. This may be related to limited recognition of efficacy of this strategy, or physicians' perception of what patients value and prefer. Decisions on preferred route of treatment administration are understandably patient-sensitive, with inter-individual variability. In survey studies and focused group-based qualitative studies in patients with mild-moderate UC, efficacy, speed of onset of action and avoidance of immunosuppressive agents are highly valued, as is route of administration.[98–100] While patients generally prefer oral administration over rectal therapy, they are often open to rectal therapy as adjunct to be used during acute flares,

especially if able to avoid immunosuppressive therapy. Appropriate dosing of mesalamine is another area of considerable variability. While several early trials used low-dose mesalamine (<2g/d) both for induction and maintenance of remission, our findings clearly demonstrate that this dose has significantly lower efficacy. While traditional meta-analyses had shown only a small benefit (6% lower odds of failing to induce remission) of high-dose mesalamine (>3g/d) over standard-dose (2–3g/d) mesalamine, especially in a subset of patients with moderate disease, our network meta-analysis suggests that the effect estimate may be larger (22% lower risk of failing to achieve remission). We estimate that, with median placebo rates of induction of remission of 13% in this population, approximately 33% and 26% patients treated with oral high- or standard-dose mesalamine may be expected to achieve remission, respectively. At the same time, our findings do not support superiority of high-dose mesalamine over standard-dose mesalamine for maintenance of remission. While RCTs on dose de-escalation from high- to standard-dose mesalamine have not been performed, our findings may support a cautious attempt at de-escalating patients with mild-moderate UC in clinical and endoscopic remission. This will help decrease healthcare costs associated with 5-ASA use in patients with UC.

Though traditional meta-analysis based on two trials comparing olsalazine vs. placebo failed to demonstrate superiority of diazo-bonded 5-ASA over placebo due to small sample size and low event rate, our network meta-analysis, by combining direct and indirect evidence, confirms superiority of diazo-bonded 5-ASA over placebo.

Our findings confirmed that budesonide MMX 9mg is a safe and effective alternative in inducing remission in patients with mild-moderate UC. However, it was not more effective than optimized 5-ASA, and given inferior tolerability and inability to use this for long-term maintenance, it may not be appropriate first-line medication. Studies have suggested a small benefit of budesonide MMX when added to 5-ASA in patients with persistent mild-moderate UC despite 5-ASA. Given superior tolerability to oral prednisone, it may be an appropriate alternative to prednisone in this instance.

Besides inherent limitations of individual trials, there are limitations to our analyses. First, for some comparisons, head-to-head trials were limited, especially for maintenance of remission. In some of these analyses, network incoherence was observed, especially for comparisons between low-dose mesalamine, diazo-bonded 5-ASA and sulfasalazine. Second, trials did not adequately stratify based on whether patients were 5-ASA-naïve or if they had previously been treated with 5-ASA; while in moderate-severe UC it is well-recognized that patients with non-response to tumor necrosis factor antagonists, or those being re-treated with the same agent after a drug holiday, have lower likelihood of response to a second biologic agent, it is unknown whether the same applies to mild-moderate UC, and how it may influence trial outcomes. Pooled analyses of individual participant data from clinical trials may help inform comparative efficacy of different interventions, stratified by prior exposure to 5-ASA therapy; similarly, individual participant data pooled analysis would also be able to inform efficacy of different interventions in patients with left-sided colitis vs. extensive colitis. Third, different trials utilized different disease activity indices and there were subtle differences in outcome definitions. However, most trials relied on a combination of improvement in clinical and endoscopic outcomes. Fourth, we did not

specifically study comparative efficacy of interventions for left-sided colitis. In these patients, rectal 5-ASA therapy alone may be as effective, or even more effective than oral therapy.

Contextualizing findings on comparative efficacy and tolerability, coupled with patients' values and preference as well cost and resource utilization considerations, we suggest a treatment algorithm for patients with mild-moderate UC. Patients with mild UC are likely to achieve remission with standard-dose mesalamine or diazo-bonded 5-ASA; a subset of patients, particularly those with more moderately active disease, or in area where high unit dose forms of mesalamine are available at a low cost, individual physicians may reasonably decide to use high-dose oral mesalamine for induction of remission. In patients with extensive colitis, rectal 5-ASA may be added either upfront to standard- or high-dose oral mesalamine or in 4–6 weeks in a subset of patients with suboptimal response to oral therapy. Likewise, budesonide MMX may be considered as monotherapy or in addition to 5-ASA therapy in patients with moderately active disease, either upfront or in case of suboptimal response to optimized 5-ASA therapy. Low-dose mesalamine is not recommended for induction of remission. While sulfasalazine has inferior tolerability and efficacy (in part due to limited ability to dose-escalate), it may be considered in a small subset of patients with mild extra-intestinal articular manifestations. For maintenance of remission, standard-dose mesalamine and diazo-bonded 5-ASA may be preferred options; high-dose mesalamine with or without rectal 5-ASA are no more effective than standard-dose mesalamine, and consideration should be made to cautiously de-escalate patients who required high-dose mesalamine for induction of remission to standard-dose, after 6–12 months.

In conclusion, based on a systematic review and network meta-analysis of 48 RCTs of induction therapy and 28 RCTs of maintenance therapy, we identified combined oral and rectal 5-ASA and high-dose mesalamine may be most likely to induce remission, and standard-dose mesalamine and diazo-bonded 5-ASA may be effective maintenance therapies for the majority of patients with mild-moderate extensive UC. Future studies on optimal risk stratification of patients with mild-moderate disease activity as having mild vs. severe disease (low vs. high risk of colectomy and adverse outcomes) is warranted to inform step therapy vs. early high-dose 5-ASA with or without rectal 5-ASA. Similarly, studies informing when to escalate patients with mild-moderate disease activity from optimized 5-ASA to immunosuppressive agents are warranted, especially for patients who require intermittent corticosteroids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Cosntext

Evidence before this study

We searched PubMed from inception through May 2018 for previously published meta-analysis on pharmacological interventions for mild-moderate ulcerative colitis using the search terms 'ulcerative colitis' combined with 'treatment'. Previous traditional pairwise meta-analyses provide a limited synthesis of comparative efficacy of different interventions, limited only to head-to-head trials, without incorporating indirect evidence. Additionally, the quality of this evidence has not been critically examined, which may inform clinical guidelines.

Added value of this study

Our study provides the first network meta-analysis of all pharmacological interventions for management of mild-moderate ulcerative colitis, with systematic assessment of quality of the evidence using GRADE methodology. Through a systematic review with network meta-analysis, including 48 RCTs (8020 participants) comparing 8 active interventions for induction of remission, and 28 RCTs (4218 participants) comparing 6 active interventions for maintenance of remission in patients with left-sided or extensive UC, we are able to inform the treatment approach in these patients. We found that for induction of remission, combined oral and rectal 5-ASA is the most effective treatment strategy, followed by high-dose mesalamine (moderate confidence in estimates); standard-dose mesalamine is comparable to diazo-bonded 5-ASA, but superior to sulfasalazine. For maintenance of remission, standard- and high-dose mesalamine are comparable (low confidence in estimates), and superior to low-dose mesalamine (high confidence in estimates). Budesonide MMX is not more effective than combined oral and rectal 5-ASA or high-dose mesalamine and has inferior tolerability.

Implications of all the available evidence

Contextualizing findings on comparative efficacy and tolerability, coupled with patients' values and preference as well cost and resource utilization considerations, our findings can directly inform treatment guidelines. Patients with mild UC are likely to achieve remission with standard-dose mesalamine or diazo-bonded 5-ASA; a subset of patients, particularly those with more moderately active disease, or in area where high unit dose forms of mesalamine are available at a low cost, physicians may reasonably decide to use high-dose oral mesalamine for induction of remission. In patients with extensive colitis, rectal 5-ASA may be added either upfront to standard- or high-dose oral mesalamine or in 4–6 weeks in a subset of patients with suboptimal response to oral therapy. Likewise, budesonide MMX may be considered as monotherapy or in addition to 5-ASA therapy in patients with moderately active disease, either upfront or in case of suboptimal response to optimized 5-ASA therapy. For maintenance of remission, standard-dose mesalamine and diazo-bonded 5-ASA may be preferred options; high-dose mesalamine with or without rectal 5-ASA are no more effective than standard-dose mesalamine, and consideration should be made to cautiously de-escalate patients who required high-dose mesalamine for induction of remission to standard-dose, after 6–12 months.
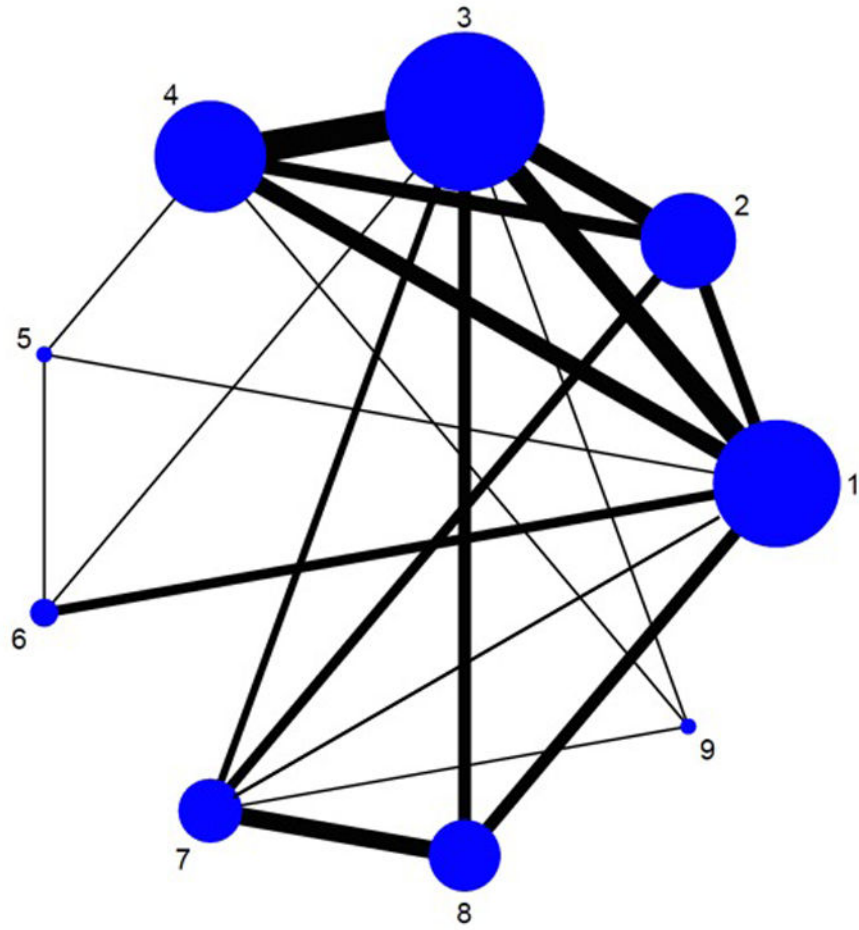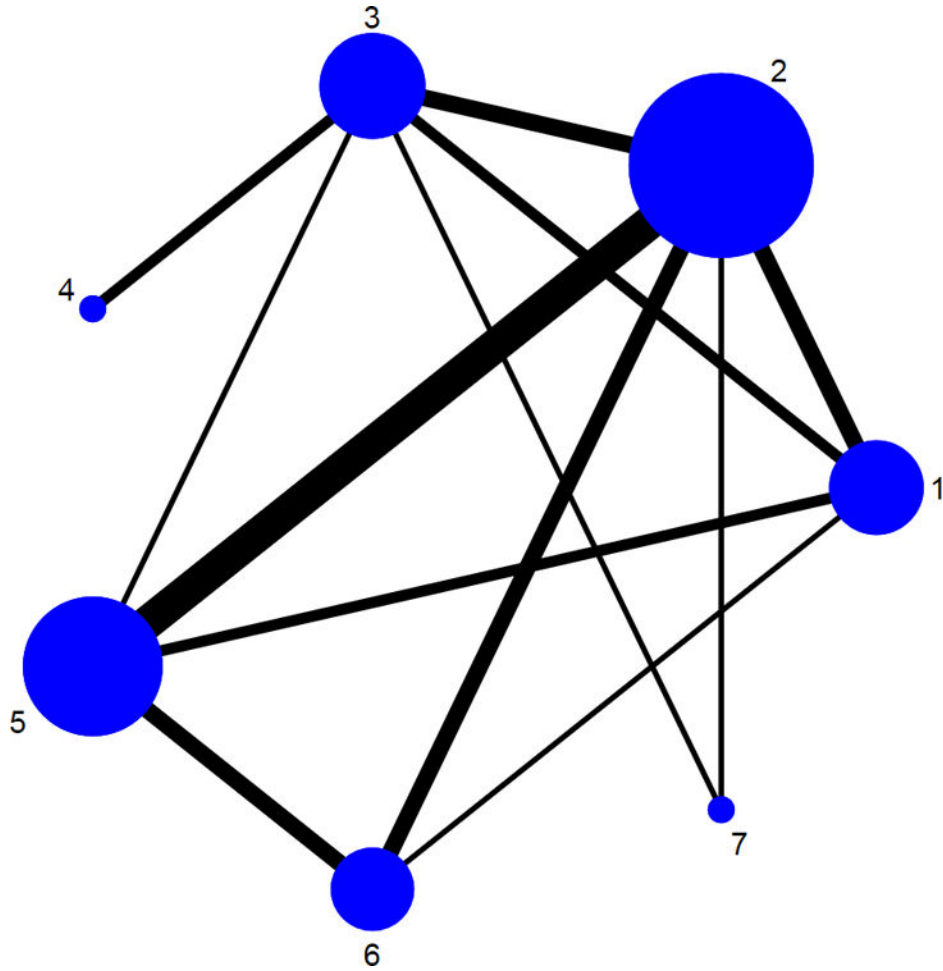
Figure 1.
Network of included studies with the available direct comparisons for (A) induction and (B) maintenance of clinical remission in patients with mild-moderate ulcerative colitis. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively. In panel A, number corresponds to 1: Placebo/Control, 2: Low-dose mesalamine (<2g), 3: Standard dose mesalamine (2–3g), 4: High-dose mesalamine (>3g), 5: Controlled ileal relelase budesonide, 6: Budesonide MMX, 7: Sulfsalazine, 8: Diazo-bonded 5-aminosalicylates (olsalazine/ balsalazide), 9: Oral + Rectal 5-aminosalicylates. In panel B, number corresponds to 1: Placebo/Control, 2: Low-dose mesalamine (<2g), 3: Standard dose mesalamine (2–3g), 4: High-dose mesalamine (>3g), 5: Sulfsalazine, 6: Diazo-bonded 5-aminosalicylates (olsalazine/balsalazide), 7: Oral + Rectal 5-aminosalicylates.

Failure to Induce Remission (vs. placebo)

	OR (95% CI)
Oral + rectal 5-ASA	0.21 (0.11-0.40)
Diazo-bonded 5-ASA	0.47 (0.35-0.62)
Sulfasalazine	0.81 (0.57-1.17)
Budesonide MMX	0.42 (0.29-0.62)
CIR-Budesonide	0.68 (0.43-1.07)
High-dose mesalamine (>3g/d)	0.40 (0.31-0.51)
Standard-dose mesalamine (<2g/d)	0.51 (0.40-0.64)
Low-dose mesalamine (<2g/d)	0.66 (0.46-0.90)

Failure to Induce Clinical Remission

Failure to Induce Remission (vs. standard-dose mesalamine)

	OR (95% CI)
Oral + rectal 5-ASA	0.41 (0.22-0.77)
Diazo-bonded 5-ASA	0.92 (0.71-1.19)
Sulfasalazine	1.61 (1.16-2.23)
Budesonide MMX	0.84 (0.55-1.26)
CIR-Budesonide	1.34 (0.86-2.07)
High-dose mesalamine (>3g/d)	0.78 (0.66-0.93)
Low-dose mesalamine (<2g/d)	1.30 (1.00-1.69)

Failure to Induce Clinical Remission
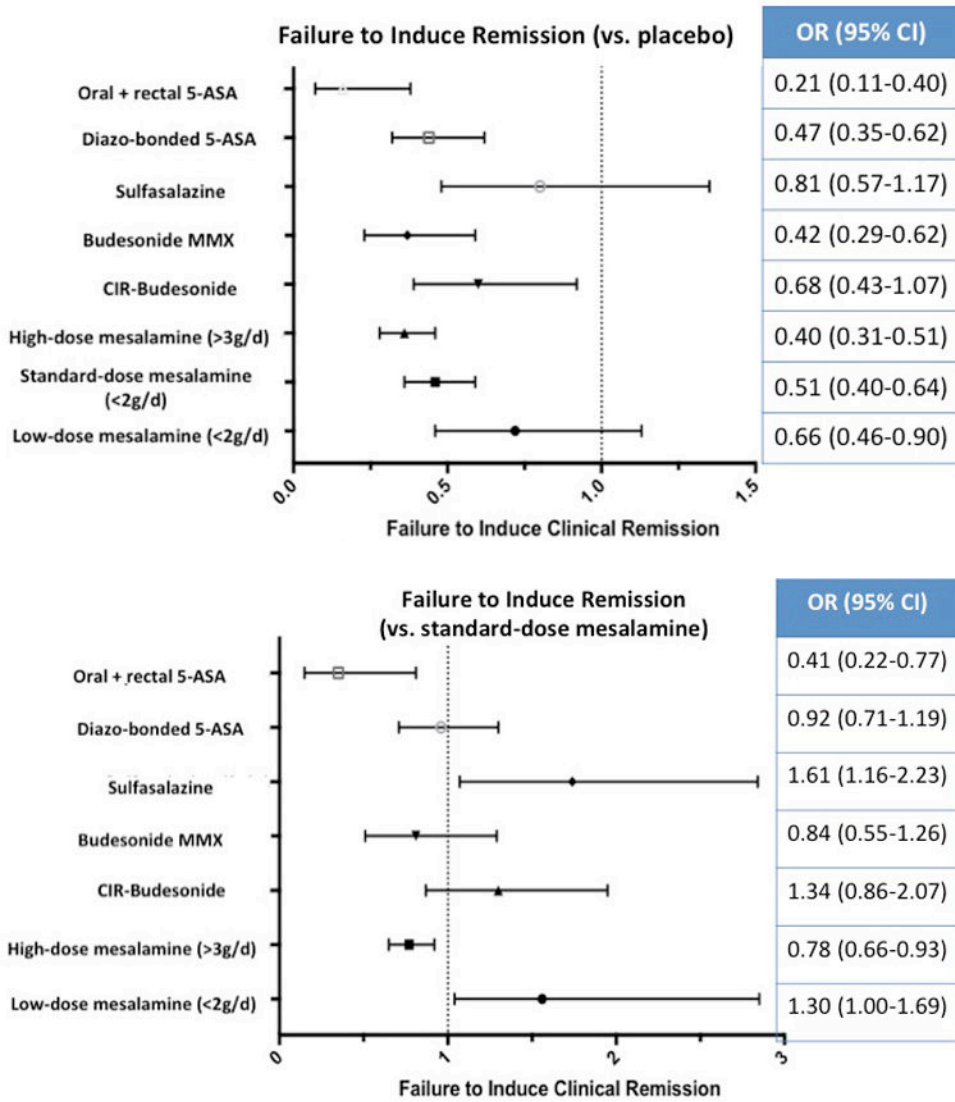
Figure 2.
Comparative efficacy of different interventions for failing to induce remission in patients with mild-moderate ulcerative colitis against (A) placebo and (B) standard-dose (2–3g/d) mesalamine, based on network meta-analysis

	Failure to induce clinical remission						
Oral + Topical 5-ASA	**0·44** (0·23 – 0·87)	**0·26** (0·13 – 0·51)	0·49 (0·24 – 1·02)	**0·39** (0·15 – 0·64)	**0·52** (0·28 – 0·97)	**0·41** (0·22 – 0·77)	**0·32** (0·16 – 0·61)
1·23 (0·36 – 4·19)	**Diazo-bonded 5-ASA**	**0·57** (0·41 – 0·80)	1·10 (0·70 – 1·74)	0·69 (0·42 – 1·13)	1·18 (0·88 – 1·58)	0·92 (0·71 – 1·19)	**0·71** (0·51 – 0·98)
0·50 (0·13 – 1·81)	**0·40** (0·20– 0·81)	**Sulfasalazine**	**1·92** (1·16 – 3·19)	1·20 (0·71 – 2·05)	**2·05** (1·44 – 2·92)	**1·61** (1·16 – 2·23)	1·23 (0·89 – 1·71)
0·64 (0·46 – 4·32)	**0·52** (0·28 – 0·98)	1·29 (0·55 – 3·04)	**Budesonide MMX 0·9**	0·63 (0·38 – 1·04)	1·07 (0·70 – 1·62)	0·84 (0·55 – 1·26)	0·64 (0·40 – 1·02)
0·68 (0·19 – 2·21)	0·55 (0·27 – 1·13)	1·37 (0·54 – 3·44)	1·06 (0·56 – 2·00)	**CIR Budesonide**	**1·71** (1·13 – 2·57)	1·34 (0·86 – 2·07)	1·03 (0·63 – 1·68)
1·48 (0·49 – 4·48)	1·20 (0·71 – 2·02)	**2·99** (1·38 – 6·46)	**2·31** (1·33 – 3·99)	**2·18** (1·20 – 3·96)	**High-dose mesalamine (>3g/d)**	**0·78** (0·66 – 0·93)	**0·60** (0·45 – 0·80)
1·13 (0·36 – 3·58)	0·91 (0·59 – 1·43)	**2·27** (1·10 – 4·71)	**1·76** (1·04 – 2·97)	1·66 (0·89 – 3·01)	0·76 (0·55 – 1·06)	**Standard dose mesalamine (2-3g/d)**	**0·77** (0·59 – 1·00)
0·69 (0·19 – 2·50)	0·56 (0·28 – 1·11)	1·39 (0·72 – 2·71)	1·08 (0·50 – 2·31)	1·02 (0·44 – 2·34)	**0·47** (0·24 – 0·90)	0·61 (0·33 – 1·14)	**Low-dose mesalamine (<2g/d)**

(Left column label, rotated: Tolerability (discontinuation of therapy))

Figure 3. Comparative efficacy and tolerability of induction therapy for mild-to-moderate ulcerative colitis.

Comparisons should be read from left to right. Odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Bold numbers with darker background are statistically significant; values that were borderline significant are in a lighter shade. For risk of failing to achieve clinical remission, odds ratio <1 favors row-defining treatment. For risk of drug discontinuation (tolerability), odds ratio <1 favors column-defining treatment. The numbers in parentheses represents 95% confidence intervals

	Failure to maintain clinical remission					
Placebo	3·85 (1·56 – 9·49)	2·17 (1·46 – 3·21)	2·72 (1·91 – 3·86)	3·50 (2·19 – 5·57)	3·02 (2·28 – 4·01)	2·18 (1·62 – 2·84)
0·58 (0·03 – 9·86)	Oral + Rectal 5-ASA	0·56 (0·22 – 1·43)	0·71 (0·28 – 1·76)	0·91 (0·35 – 2·38)	0·78 (0·32 – 1·91)	0·57 (0·24 – 1·35)
0·40 (0·20 – 0·77)	1·47 (0·08 – 26·06)	Diazo-bonded 5-ASA	1·25 (0·90 – 1·74)	1·61 (0·93 – 2·80)	1·40 (0·93 – 2·10)	1·01 (0·71 – 1·43)
0·45 (0·20 – 1·02)	1·30 (0·07 – 23·86)	0·88 (0·47 – 1·64)	Sulfasalazine	1·29 (0·77 – 2·15)	1·11 (0·78 – 1·59)	0·80 (0·60 – 1·07)
0·22 (0·06 – 0·84)	2·60 (0·12 – 57·06)	1·76 (0·42 – 7·31)	2·00 (0·45 – 8·97)	High-dose 5-ASA (>3g/d)	0·86 (0·60 – 1·25)	0·62 (0·40 – 0·97)
0·49 (0·35 – 0·68)	1·20 (0·07 – 19·99)	0·81 (0·43 – 1·52)	0·92 (0·42 – 2·03)	0·46 (0·13 – 1·65)	Standard-dose 5-ASA (2-3g/d)	0·72 (0·57 – 0·92)
0·59 (0·42 – 0·84)	0·98 (0·06 – 16·36)	0·67 (0·37 – 1·19)	0·76 (0·36 – 1·60)	0·38 (0·10 – 1·39)	0·82 (0·64 – 1·05)	Low-dose 5-ASA (<2g/d)

(Left-side vertical label: Tolerability (discontinuation of therapy))

Figure 4. Comparative efficacy and tolerability of maintenance therapy for mild-to-moderate ulcerative colitis.

Comparisons should be read from left to right. Odds ratio for comparisons are in the cell in common between the column-defining and row-defining treatment. Bold numbers with darker background are statistically significant; values that were borderline significant are in a lighter shade. For risk of failing to achieve clinical remission, odds ratio <1 favors row-defining treatment. For risk of drug discontinuation (tolerability), odds ratio <1 favors column-defining treatment. The numbers in parentheses represents 95% confidence intervals

Table 1.

GRADE Quality of Evidence of different interventions for induction and maintenance of clinical remission in patients with mild-moderate ulcerative colitis, based on direct meta-analysis and network meta-analysis

	Induction of Remission		Maintenance of Remission	
	Direct	Network	Direct	Network
All interventions vs. Placebo				
Low-dose mesalamine	Moderate[1]	Moderate	High	High
Standard-dose mesalamine	High	High	High	High
High-dose mesalamine	High	High	-	Moderate
CIR Budesonide	Low[1,2]	Moderate	N/A	N/A
Budesonide MMX	Moderate[1]	Moderate	N/A	N/A
Sulfasalazine	Moderate[1]	Moderate	Low[1,3]	Low
Diazo-bonded 5-ASA	Moderate[1]	Moderate	Low[1,3]	Moderate
Oral + rectal 5-ASA	-	Moderate	-	Low
All interventions vs. Low-dose mesalamine				
Standard-dose mesalamine	High	High	High	High
High-dose mesalamine	High	High	-	Moderate
CIR Budesonide	-	Low[4]	N/A	N/A
Budesonide MMX		Moderate	N/A	N/A
Sulfasalazine	Modserate[1]	Low[4]	Low[4]	Moderate
Diazo-bonded 5-ASA	-	Low	Moderate[1]	Low
Oral + rectal 5-ASA	-	Moderate	Low[4]	Low
All interventions vs. Standard-dose mesalamine				
High-dose mesalamine	Moderate[1]	High	Low[4]	Low
CIR Budesonide	-	Low[4]	N/A	N/A
Budesonide MMX	Low[1,2]	Low	N/A	N/A
Sulfasalazine	Moderate	Moderate	Low[4]	Low
Diazo-bonded 5-ASA	Low[1,3]	Low[4]	-	Low
Oral + rectal 5-ASA	Moderate[1]		Low[1,6]	Low
All interventions vs. High-dose mesalamine				
CIR Budesonide	Moderate[1]	Moderate	N/A	N/A
Budesonide MMX	-	Low	N/A	N/A
Sulfasalazine	-	Moderate	-	Low
Diazo-bonded 5-ASA	-	Low	-	-
Oral + rectal 5-ASA	Low[4]	Moderate	-	Low

	Induction of Remission		Maintenance of Remission	
	Direct	Network	Direct	Network
All interventions vs. CIR Budesonide				
Budesonide MMX	Low[1,2]	Low	N/A	N/A
Sulfasalazine	-	Low	N/A	N/A
Diazo-bonded 5-ASA	-	Low	N/A	N/A
Oral + rectal 5-ASA	-	Moderate	N/A	N/A
All interventions vs. Budesonide MMX				
Sulfasalazine	-	Moderate	N/A	N/A
Diazo-bonded 5-ASA	-	Low[4]	N/A	N/A
Oral + rectal 5-ASA	-	Low	N/A	N/A
All interventions vs. Sulfasalazine				
Diazo-bonded 5-ASA	Moderate[1]	Moderate	Low[1,5]	Low
Oral + rectal 5-ASA	Moderate[1]	Moderate	-	Low
All interventions vs. Diazo-bonded 5-ASA				
Oral + rectal 5-ASA	-	Moderate	-	Low

[1] Rated down for imprecision

[2] Risk of bias

[3] Rated down for inconsistency

[4] Rated down for very serious imprecision

[5] Rated down for indirectness (very limited data on balsalazide which may be the preferred diazo-bonded 5-ASA given higher intolerability with olsalazine due to diarrhea)

[6] Rated down for indirectness (comparator group received low-dose mesalamine, whereas combined mesalamine amount in intervention group exceeded 2g)