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TITLE PAGE

Title: Efficacy of Oral, Topical, or Combined Oral and Topical 5-Aminosalicylates, in Ulcerative Colitis: Systematic Review and Network Meta-Analysis

Short running head: 5-Aminosalicylates in Ulcerative Colitis: Network Meta-Analysis

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Key words: 5-aminosalicylates, 5-ASAs, inflammatory bowel disease, ulcerative colitis, network, meta-analysis.

Abbreviations:

5-ASAs	5-aminosalicylates
AGA	American Gastroenterological Association
CI	confidence interval

ECCO	European Crohn's and Colitis Organisation
RCT	randomised controlled trial
RR	relative risk
UC	ulcerative colitis

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ABSTRACT

Background: 5-aminosalicylates (5-ASAs) are the mainstay of treatment for ulcerative colitis (UC). The optimum preparation, dose, and route of administration for UC remains unclear. We conducted a network meta-analysis to examine this issue.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials from inception to December 2020. We included randomised controlled trials (RCTs) comparing oral, topical, or combined oral and topical 5-ASAs, with each other, or placebo for induction of remission or prevention of relapse of UC. Results were reported as pooled relative risks (RRs) with 95% confidence intervals (CIs) to summarize effect of each comparison tested, with treatments ranked according to P-score.

Results: We identified 40 RCTs for induction of remission and 23 for prevention of relapse. Topical mesalazine (P-score 0.99), or oral and topical mesalazine combined (P-score 0.87) ranked first and second for clinical and endoscopic remission combined. Combined therapy ranked first in trials where ≥50% of patients had left-sided/extensive disease, and topical mesalazine first in trials where ≥50% of patients had proctitis/proctosigmoiditis. High-dose (≥3.3g/day) oral mesalazine ranked third in most analyses, with the most trials and most patients. For relapse of disease activity, combined therapy and high-dose oral mesalazine ranked first and second, with topical mesalazine third. 5-ASAs were safe and well-tolerated, regardless of regimen.

Conclusions: Our results support previous evidence, however, higher doses of oral mesalazine had more evidence for induction of remission than combined therapy and were significantly more efficacious than lower doses. Future RCTs should better establish the role of combined therapy for induction of remission, as well as optimal doses of oral 5-ASAs to prevent relapse.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that causes continuous mucosal inflammation of the lower gastrointestinal tract, commencing in the rectum and extending proximally for a variable extent.[1,2] Burden of disease studies report an estimated prevalence of 1 million people in the USA and 2.5 million in Europe.[3] UC follows a relapsing and remitting course, with sufferers experiencing intermittent flares of disease activity, the majority of which are treated with medical therapy. 5-aminosalicylates (5-ASAs) are one of the oldest drugs used for the treatment of UC patients. Although the first use of sulfasalazine in UC was reported in 1941,[4] its acceptability in clinical practice has been limited by various side effects, thought to arise from the sulfapyridine moiety, including nausea, vomiting, anemia, fever, and headaches.[5] Thus, in the 1980s the advent of the 5-ASA moiety alone, mesalazine,[6] which has a better side effect profile, changed the landscape of treatment for UC. 5-ASAs without the sulfapyridine moiety have since become the mainstay of therapy for the induction of remission in mild to moderately active UC,[7] as well as for the prevention of relapse of disease activity in quiescent UC.

Over 90% of patients receive a 5-ASA within the first year of diagnosis, with between 60% and 90% continuing their use up to 15 years.[7] Importantly, 5-ASA medications can be administered both orally and topically. Previous meta-analyses show that oral, topical, and combined oral and topical 5-ASAs are efficacious for both induction of remission in UC and prevention of relapse of disease activity.[8-10] These meta-analyses suggest that higher doses of oral 5-ASAs are more efficacious than lower doses of oral 5-ASAs for inducing remission and for preventing relapse,[8] that combined oral and topical 5-ASAs are more efficacious than oral 5-ASAs for induction of remission,[8] and that topical 5-ASAs are more efficacious than oral 5-ASAs for preventing relapse of quiescent disease.[8] Current guidelines recommend topical 5-ASAs for active proctitis, and combined therapy with both oral and topical 5-ASAs for mildly to moderately active left-sided colitis, and more extensive disease.[11] Moreover, they suggest that extensive UC, of mild-to-moderate activity, can be approached with standard-dose (defined as 2g to 3g/day) mesalazine or

diazo-bonded 5-ASA (e.g. balsalazide), to induce remission.[12] Regarding prevention of relapse, current European Crohn's and Colitis Organization (ECCO) guidelines state that rectal mesalazine be used as first-line maintenance in proctitis and as an alternative in left-sided colitis. A combination of oral and topical mesalazine can be used as second-line maintenance.[11]

Despite these meta-analyses, and the recommendations of contemporaneous guidelines, there are few head-to-head trials comparing different routes of administration of 5-ASAs, and there have been further studies published comparing differing doses of oral 5-ASAs published in the intervening years. As a result, the relative efficacy of oral, topical, or combined oral and topical 5-ASAs in inducing remission in mild to moderate UC, and in preventing relapse of quiescent UC, is unclear. In addition, prior meta-analyses have not assessed the efficacy of 5-ASAs according to disease distribution. Consequently, decision making regarding dose and route of 5-ASA therapy is based on older studies. One of the main drawbacks of studies exploring the use of 5-ASAs is the heterogeneity in dosing, regimen, and 5-ASA used. This makes direct comparison between studies difficult. Network meta-analysis may be able to resolve some of this uncertainty, because the methodology employed allows indirect, as well as direct, comparisons to be made across different RCTs, increasing the number of participants' data available for analysis. In addition, this technique allows a credible ranking system of the likely efficacy of different drugs to be developed, which can aid clinical decision-making. A prior network meta-analysis of induction therapies for mild to moderately active UC reported that combined oral and topical, and high-dose oral 5-ASAs were ranked highest,[13] but this network meta-analysis was limited to induction of remission, and only included patients with left-sided or extensive disease.

We have therefore performed a network meta-analysis to evaluate the efficacy of oral, topical, or combined oral and topical 5-ASAs, compared with each other or with placebo in terms of induction of remission for active UC, and prevention of relapse for quiescent UC. We restricted our network meta-analysis to mesalazine and balsalazide, because olsalazine is rarely used and the use of sulfasalazine is limited by tolerability.[14,15]

METHODS

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (1946 to the 2nd December 2020), EMBASE and EMBASE classic (1947 to the 2nd December 2020), the Cochrane central register of controlled trials (Issue 2, December 2020), and the Cochrane Inflammatory Bowel Disease Group Specialised Trials Register. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2006 and 2020 to identify studies published only in abstract form.

RCTs examining the efficacy of oral 5-ASAs, topical 5-ASAs, or combined oral and topical 5-ASAs, versus each other, or versus a placebo, in adult patients (>90% of participants over the age of 16 years) with active or quiescent UC were eligible for inclusion (Table 1). The first period of crossover RCTs was also eligible for inclusion. Duration of therapy had to be at least 14 days for induction of remission trials in active UC, and at least 6 months for prevention of relapse trials in quiescent UC. Trials using any dose of 5-ASAs were considered eligible. Studies had to report either an assessment of failure to achieve remission in active UC, or occurrence of relapse of disease activity in quiescent UC, at the last point of follow-up. For failure to achieve induction of remission, trials had to report one or more of the following endpoints: a composite of clinical and endoscopic remission; clinical remission; endoscopic remission; or histological remission. Trials of 5-ASAs in active UC that reported an improvement in disease activity as their only outcome were not eligible for inclusion. For relapse of disease activity, trials had to report one or more of the following endpoints: clinical and endoscopic relapse combined; clinical relapse; endoscopic relapse; or histological relapse. First and senior authors of the studies were contacted to provide additional information on trials where required. The study protocol was published on the

PROSPERO international prospective register of systematic reviews (registration number CRD42020185839). Ethical approval for this evidence synthesis was not required.

Studies were identified with the terms *ulcerative colitis* or *colitis* (both as medical subject headings and as free text terms). These were combined using the set operator AND with studies identified with the terms: *mesalamine*, or *aminosalicylic acid* (both as medical subject headings and as free text terms), or the following free text terms: *balsalazide*, *mesalazine*, *pentasa*, *5-ASA*, *5ASA*, *5-aminosalicylic$*, *5-aminosalicylate$*, *5aminosalicylic$*, or *5aminosalicylate$*. There were no language restrictions. We screened the titles and abstracts of all citations identified by our search for potential suitability and retrieved those that appeared relevant to examine them in more detail. We performed a recursive search, using the bibliographies of all eligible articles. We translated foreign language articles, where required. If a study appeared potentially eligible, but did not report the data required, we planned to contact authors to obtain supplementary information. We performed eligibility assessment independently. This was done by two investigators (ACF and BB), using pre-designed eligibility forms. We resolved any disagreements by consensus and measured the degree of agreement with a kappa statistic.

Outcome Assessment

The primary outcomes assessed were the efficacy of oral 5-ASAs, topical 5-ASAs, or combined oral and topical 5-ASAs, versus each other, or placebo, in terms of failure to achieve remission in active UC, and occurrence of relapse of disease activity in quiescent UC. Secondary outcomes included adverse events occurring due to therapy, including total numbers of adverse events, and adverse events leading to study withdrawal.

Data Extraction

Due to the large number of RCTs, data were extracted independently by one of three investigators (BB, JPS, and MNQ) on to a Microsoft Excel spreadsheet (XP professional edition;

Microsoft, Redmond, WA) as dichotomous outcomes (remission or failure of remission in active UC, and relapse or no relapse of disease activity in quiescent UC). A second person (ACF) data extracted all trials independently, with results of data extraction compared and any disagreements resolved by consensus. We planned to extract these data for each trial according to the dose of oral or topical 5-ASA used. However, after an initial analysis, there was no dose-response effect of topical 5-ASAs, so data for these trials were pooled together irrespective of dose. For oral 5-ASAs, we classed dosages of mesalazine of ≤1.6g/day as low-dose, 1.7g to 3.2g/day as standard-dose, and ≥3.3g/day as high-dose. For oral balsalazide, which has a lower total dose of 5-ASA (1g balsalazide delivers 0.35g 5-ASA), this was as follows: ≤4.5g/day as low-dose and ≥4.6g/day as standard-dose.[16] In addition, we extracted the following clinical data for each trial, where available: number of centres, country of origin, distribution of UC, endpoints used to define remission or relapse, dosage, route, and schedule of 5-ASA used, duration of therapy, and number of individuals incurring each (or any) of the adverse events of interest. Where individual trials used more than one endpoint to define failure of induction of remission or relapse, we extracted data separately for each of the endpoints reported. We extracted data as intention-to-treat analyses, with all dropouts assumed to be treatment failures (i.e., failed to achieve remission in active UC trials or disease activity relapsed in quiescent UC trials), wherever trial reporting allowed this. If the number of dropouts was not clear from the original article, we extracted data only for patients with reported evaluable data.

Quality Assessment and Risk of Bias

We used the Cochrane Risk of Bias tool to assess the quality of studies.[17] Two investigators (ACF and BB) assessed study quality independently, with disagreements resolved by discussion. For all RCTs we recorded the method used to generate the randomisation schedule and conceal treatment allocation, whether participants, personnel, and outcome assessments were blinded, whether there was evidence of incomplete patient outcome data, and whether there was evidence of selective reporting of patient outcomes.

Data Synthesis and Statistical Analysis

We performed a network meta-analysis using the frequentist model with the statistical package netmeta (version 0.9-0), in R (version 3.4.6) to compare (directly and indirectly) the efficacy and safety of each treatment of interest across studies. The results were reported according to the PRISMA extension statement for network meta-analyses.[18] Network meta-analysis results usually give a more precise estimate of the relative efficacy and safety than results from standard pairwise analyses,[19,20] and allow treatments to be ranked in terms of efficacy to help inform clinical decisions.[21]

We examined the symmetry and geometry of the data by producing a network plot, with node sizes corresponding to the number of study participants, and connection sizes corresponding to the number of studies for each treatment. We planned to generate comparison-adjusted funnel plots to evaluate publication bias and small study bias for all available treatment comparisons, where sufficient studies (≥10) existed.[22] These are scatterplots of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias or small-study bias.[23] For each treatment, we generated a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarize the effect of each comparison tested using a random effects model as a conservative estimate. The RR of failure to achieve remission and RR of relapse of disease activity were used as the measure of treatment efficacy, whereby if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of one treatment over another, or over placebo.

We assessed global statistical heterogeneity across all comparisons using the I^2 measure with the netmeta statistical package. The I^2 measure of heterogeneity ranges from 0% to 100% whereby a value of 25% to 49% indicates low study heterogeneity, 50% to 74% indicates moderate heterogeneity, and ≥75% indicates high heterogeneity.[24] We ranked treatments according to the P-score, which generates a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and they measure the extent of certainty that one

treatment is better according to any given endpoint than another treatment as an average over all other competing treatments.[25] The higher the P-score, the greater the probability of the treatment being ranked as best,[25] but the magnitude of the P-score should also be considered because, as the mean value is always 0.5, if individual treatments cluster around this value, it is likely that they have similar efficacies. However, when interpreting the results, it is also important to take the RR and corresponding 95% CI for each comparison into account, rather than relying on rankings alone.[26] In our primary analysis, we pooled data for all trials, irrespective of disease distribution, but we conducted a subgroup analysis of the efficacy of 5-ASAs in only trials that recruited ≥50% of patients with proctitis or proctosigmoiditis, or only trials in which ≥50% or more of patients had left-sided or extensive colitis. Trials that included equal numbers of patients with proctitis or proctosigmoiditis and patients left-sided or extensive colitis contributed to both these analyses.

RESULTS

The literature search identified 18,314 citations, of which 18,135 were excluded on review of the title and abstract (Figure 1). From these we identified 181 articles that appeared to be relevant to the study question. In total, 69 of these articles,[6,16,27-93] reporting on 67 separate RCTs, and containing 11.733 subjects with UC, fulfilled the eligibility criteria. Two of these articles were dual publications,[29,53] but provided extra data on three other studies.[28,40,52] Agreement between investigators for assessment of study eligibility was excellent (kappa statistic = 0.85). There were 43 RCTs, reported in 45 articles, comparing the efficacy of oral and topical 5-ASAs with each other and/or placebo in inducing remission of active UC,[6,27-70] and 24 trials examining efficacy in preventing relapse of quiescent UC.[16,71-93] However, four of these trials were excluded, ultimately, from our reported analyses, as they only compared one dose of topical 5-ASA with another, and we pooled all topical 5-ASA treatment arms together.[27,47,61,71] Detailed characteristics of all included studies included in our analyses are provided in Supplementary Tables 1 and 2. Patients were allocated to active therapy or placebo as described in Supplementary Tables 3 and 4. All trials, except four, were published in full.[37,68,70,76] Risk of bias for all included trials is reported in Supplementary Tables 5 and 6; only eight were at low risk of bias across all domains.[6,33,35,47,65,66,90,91] We provide data concerning histological remission and adverse events in the Supplementary Materials.

Failure to Achieve Induction of Remission

Forty RCTs reported data concerning efficacy of 5-ASAs in the induction of remission of active UC.[6,28,30-46,48-52,54-60,62-70] Thirteen RCTs recruited ≥50% of patients with left-sided colitis and extensive colitis,[6,39,42,52,55,57,58,62,63,64,67,69,70] 16 RCTs recruited ≥50% of patients with proctitis and proctosigmoiditis,[28,30-33,35,36,40,41,43-45,50,54,66,68] and six studies recruited equal numbers of patients with left-sided colitis and extensive colitis or proctitis and proctosigmoiditis.[34,49,51,56,59,65] Five RCTs did not report disease distribution.[37,38,46,48,60] Among 20 trials using high-dose oral

mesalazine, nine used 4.8g/day, one 4.5g/day, six 4g/day, and four 3.6g/day. Among 23 RCTs using standard-dose oral mesalazine, one used 3g/day, 17 used 2.4g/day, two used 2.4g/day or 2.25g/day, one used 2.25g/day, and two used 2g/day. Finally, among seven trials using low-dose oral mesalazine two used 1.6g/day, one 1.5g/day, two 1.2g/day, one 1g/day, and one 800mg/day.

Failure to Achieve Clinical and Endoscopic Remission

There were 25 RCTs, in 26 articles,[6,28-30,38,40,42,45,46,48,51,52,55-60,62-67,69,70] reporting on clinical and endoscopic remission. In total 4800 patients were recruited of whom 3979 were randomised to active treatment. The network plot is provided in Supplementary Figure 1A. Pooled analysis revealed low levels of statistical heterogeneity (I^2 = 43.1%). There was no evidence of funnel plot asymmetry, suggesting publication bias, or other small study effects (Supplementary Figure 1B). Topical mesalazine, combined oral and topical mesalazine, high-dose oral mesalazine, standard-dose oral mesalazine, and standard-dose balsalazide were all significantly more efficacious than placebo, but topical mesalazine alone (RR = 0.51; 95% CI 0.41 to 0.63, P-score 0.99) and combined oral and topical mesalazine (RR = 0.62; 95% CI 0.50 to 0.78, P-score 0.87), were ranked first and second respectively (Figure 2A). This means that the probability of either topical mesalazine alone or combined oral and topical mesalazine being the most efficacious when all treatments, including placebo, were compared with each other was 99% and 87% respectively. However, high-dose and standard-dose oral mesalazine had the most trials and the most patients (14 RCTs, 1411 patients and 16 trials, 1718 patients, respectively). Low-dose mesalazine and low-dose balsalazide were no more efficacious than placebo. After indirect comparison of active treatments, both topical mesalazine and combined oral and topical mesalazine were superior to all other active treatments (Figure 2B). High-dose oral mesalazine was superior to both standard and low-dose oral mesalazine.

Following sensitivity analysis based on disease distribution, there were 17 RCTs reported in 18 articles,[6,29,40,42,51,52,55-59,62-65,67,69,70] with clinical and endoscopic remission endpoints in trials recruiting ≥50% of patients with left-sided colitis or extensive colitis. Similarly there were eight

trials, reported in nine articles,[28-30,45,51,56,59,65,66] recruiting ≥50% of patients with proctitis or proctosigmoiditis. When RCTs in left-sided colitis or extensive colitis were pooled there was low heterogeneity (I^2 = 44.4%). Standard-dose oral balsalazide ranked first (RR = 0.51; 95% CI 0.33 to 0.80, P-score 0.93), combined oral and topical mesalazine second (RR = 0.62; 95% CI 0.48 to 0.80, P-score 0.83), and high-dose oral mesalazine ranked third (RR = 0.80; 95% CI 0.74 to 0.87, P-score 0.57) (Supplementary Figure 2A), but the latter in the most trials and with the largest number of patients. Topical mesalazine and low-dose oral mesalazine were no better than placebo. League ranking is provided in Supplementary Figure 2B. When trials in patients with proctitis and proctosigmoiditis were pooled there was no heterogeneity (I^2 = 0%). Topical mesalazine was ranked first (RR = 0.46; 95% CI 0.37 to 0.58, P-score 0.99) (Supplementary Figure 3A) and was superior to high-dose and standard-dose oral mesalazine (Supplementary Figure 3B).

Failure to Achieve Clinical Remission

There were 25 RCTs[31-36,39-41,43-45,48-50,54,57-60,64,65,67-69] reporting on induction of clinical remission following 5-ASA treatment. A total of 4559 patients were recruited in these studies, of whom 3696 were randomised to active treatment. The network plot is provided in Supplementary Figure 4A. When data were pooled there was low heterogeneity (I^2 = 42.7%) with no evidence of funnel plot asymmetry (Supplementary Figure 4B). Combined oral and topical mesalazine, topical mesalazine alone, high-dose oral mesalazine, standard-dose oral balsalazide, and standard-dose oral mesalazine were all significantly more efficacious than placebo (Figure 3A). Again, high-dose and standard-dose oral mesalazine had the most trials with the most patients (11 trials, 1146 patients, and 14 RCTs, 1373 patients, respectively), although there were 10 trials of topical mesalazine containing 572 patients. Combined oral and topical mesalazine was ranked first (RR = 0.43; 95% CI 0.22 to 0.80, P-score 0.91), but 95% CIs were wide, and topical mesalazine ranked second (RR = 0.53; 95% CI 0.45 to 0.61, P-score 0.83). Conversely, low-dose oral balsalazide and low-dose oral mesalazine were no more efficacious than placebo. Indirect comparison of active treatments

revealed combined oral and topical mesalazine was superior to standard-dose and low-dose oral mesalazine, and topical mesalazine alone was superior to all other active treatments, except low-dose oral balsalazide (Figure 3B). High-dose oral mesalazine was superior to low-dose oral mesalazine.

In a subgroup analysis, based on disease distribution, there were 11 RCTs,[34,39,40,49,57-59,64,65,67,69] providing clinical remission data that recruited ≥50% of patients with left-sided colitis or extensive colitis, and 16 trials[31-36,41,43-45,49,50,54,59,65,68] providing data that recruited ≥50% of patients with proctitis or proctosigmoiditis. When RCTs in left-sided colitis or extensive colitis were pooled there was borderline low heterogeneity (I^2 = 22.9%) and combined oral and topical mesalazine ranked first (RR = 0.31; 95% CI 0.12 to 0.82, P-score 0.97) (Supplementary Figure 5A), above high-dose and standard-dose oral mesalazine. However, 95% CIs were wide and the latter two had the most trials and the most patients. Topical mesalazine and low-dose oral mesalazine were no different to placebo. League ranking is provided in Supplementary Figure 5B. Combined oral and topical mesalazine was superior to all other active treatments except topical or high-dose oral mesalazine. When trials in patients with proctitis and proctosigmoiditis were pooled there was moderate heterogeneity (I^2 = 63.3%), and topical mesalazine ranked first (RR = 0.50; 95% CI 0.39 to 0.63, P-score 0.87) and was the only efficacious therapy compared with placebo (Supplementary Figure 6A). Topical mesalazine was superior to all other therapies, except combined oral and topical mesalazine and low-dose balsalazide (Supplementary Figure 6B).

Failure to Achieve Endoscopic Remission

In total, there were 23 RCTs, reported in 25 articles,[28,29,31-37,39-41,43-45,52-54,57,60,65-67,69,70] which recruited 3408 patients, 2542 of whom were randomised to active treatment, providing these data. The network plot is provided in Supplementary Figure 7A. When data were pooled there were low levels of statistical heterogeneity (I^2 = 38.2%). On visual inspection, there was evidence of funnel plot asymmetry, suggesting publication bias, or other small study effects (Supplementary Figure

7B). Combined oral and topical mesalazine, topical mesalazine alone, high-dose oral mesalazine, and standard-dose oral mesalazine were all significantly more efficacious than placebo, but combined oral and topical mesalazine (RR = 0.57; 95% CI 0.45 to 0.73, P-score 0.90) and topical mesalazine alone (RR = 0.58; 95% CI 0.51 to 0.66, P-score 0.90) were both ranked as the most efficacious relative to placebo in four RCTs (196 patients) and 11 trials (697 patients), respectively (Figure 4A), with high-dose oral mesalazine third in 10 RCTs (719 patients). Standard-dose oral balsalazide and low-dose oral mesalazine were no more efficacious than placebo. After indirect comparison of active treatments, both combined oral and topical mesalazine and topical mesalazine alone were superior to all other active treatments, except high-dose oral mesalazine (Figure 4B). High-dose oral mesalazine was superior to low-dose oral mesalazine.

After subgroup analysis according to disease distribution, there were nine RCTs reported in 11 articles,[29,34,39,40,52,53,57,65,67,69,70] providing endoscopic remission and recruiting ≥50% of patients with left-sided colitis or extensive colitis, and 14 trials, reported in 15 articles, recruiting ≥50% of patients with patients with proctitis or proctosigmoiditis.[28,29,31-36,41,43-45,54,65,66] When RCTs in left-sided colitis or extensive colitis were pooled there was minimal heterogeneity (I^2 = 15.1%); combined oral and topical mesalazine was still ranked first (RR = 0.61; 95% CI 0.47 to 0.79, P-score 0.88), with topical mesalazine second (RR = 0.64; 95% CI 0.44 to 0.95, P-score 0.74), and high-dose oral mesalazine third (RR = 0.68; 95% CI 0.60 to 0.79, P-score 0.68) (Supplementary Figure 8A). Combined oral and topical mesalazine and high-dose oral mesalazine were both superior to low-dose mesalazine (Supplementary Figure 8B). When trials in patients with proctitis and proctosigmoiditis were pooled there was moderate heterogeneity (I^2 = 57.2%), and ranking of therapies was identical (combined oral and topical mesalazine, (RR = 0.50; 95% CI 0.27 to 0.94, P-score 0.88), topical mesalazine (RR = 0.57; 95% CI 0.49 to 0.67, P-score 0.83), and high-dose oral mesalazine (RR = 0.67; 95% CI 0.49 to 0.90, P-score 0.64)) (Supplementary Figure 9A). Topical mesalazine was superior to all other therapies, except combined oral and topical mesalazine and high-dose oral mesalazine (Supplementary Figure 9B).

Relapse of Disease Activity

In total 23 RCTs reported data concerning efficacy of 5-ASAs in relapse of disease activity in quiescent UC, with a total of 4224 patients.[16,72-93] There were 3489 patients randomised to active treatment. Among two trials using high-dose oral mesalazine, one used 4.8g/day and one 4g/day. Among six RCTs using standard-dose oral mesalazine, three used 3g/day and three used 2.4g/day. Finally, among 13 trials using low-dose oral mesalazine three used 1.6g/day, one used 1.6g/day or 800mg/day, six 1.5g/day, and three 1.2g/day.

The network plot is provided in Supplementary Figure 10A. Due to insufficient numbers of trials reporting relapse of disease activity according to each of our endpoints of interest, we pooled data for all trials irrespective of definition of relapse used, with low levels of statistical heterogeneity (I^2 = 30.2%). On visual inspection, there was evidence of funnel plot asymmetry, suggesting publication bias, or other small study effects (Supplementary Figure 10B). All treatments, except standard-dose or low-dose balsalazide, were more efficacious than placebo (Figure 5A). Combined oral and topical mesalazine was ranked first (RR = 0.44; 95% CI 0.28 to 0.69, P-score 0.91), with high-dose oral mesalazine second (RR = 0.54; 95% CI 0.42 to 0.71, P-score 0.75), and topical mesalazine third (RR = 0.56; 95% CI 0.45 to 0.68, P-score 0.72). Indirect comparison of active treatments revealed that combined oral and topical mesalazine was superior to low-dose oral mesalazine and low-dose oral balsalazide, but there were no other significant differences (Figure 5B).

After subgroup analysis according to disease distribution there were 15 studies recruiting ≥50% of patients with left-sided colitis and extensive colitis[16,72,74,76-80,83,85,87,88,90-92] and eight RCTs recruiting ≥50% of patients with proctitis or proctosigmoiditis.[73,75,77,79,82,84-86] In trials of left-sided or extensive colitis there was low heterogeneity (I^2 = 33.2%). Again, all treatments, except standard-dose or low-dose balsalazide, were more efficacious than placebo, but combined oral and topical mesalazine and topical mesalazine alone were ranked first and second (RR = 0.46; 95% CI 0.28 to 0.75, P-score 0.86 and RR = 0.48; 95% CI 0.31 to 0.73, P-score 0.83 respectively)

(Supplementary Figure 11A). High-dose oral mesalazine was ranked third (RR = 0.55; 95% CI 0.42 to 0.72, P-score 0.73). Combined oral and topical mesalazine was superior to both low-dose oral mesalazine and low-dose oral balsalazide (Supplementary Figure 11B). Trials recruiting ≥50% of patients with proctitis or proctosigmoiditis only studied standard or low-dose oral mesalazine or topical mesalazine. When data were pooled there was low heterogeneity (I^2 = 45.3%). Only topical mesalazine was superior to placebo (Supplementary Figure 12A), with no difference between active therapies on indirect comparison (Supplementary Figure 12B).

DISCUSSION

In this systematic review and network meta-analysis, we compared efficacy of oral, topical, or combined oral and topical 5-ASAs, versus each other, or placebo, in terms of failure to achieve remission in active UC, as well as relapse of disease activity in quiescent UC. For failure to induce remission in active UC, through network meta-analysis, we were able to demonstrate that a combination of oral and topical mesalazine was ranked first or second, compared with other forms of mesalazine, across a variety of endpoints, and particularly in trials recruiting ≥50% of patients with left-sided or extensive disease. Topical mesalazine was ranked first for most analyses in trials that recruited ≥50% of patients with proctitis or proctosigmoiditis. However, in most analyses high-dose oral mesalazine was ranked third and had the most trials and most patients. For the most rigorous endpoint, clinical and endoscopic remission, it was superior to both standard and low-dose mesalazine. For relapse of disease activity in quiescent UC, combined oral and topical mesalazine and high-dose oral mesalazine ranked first and second, with topical mesalazine the third most efficacious treatment. However, there were few trials of combined oral and topical mesalazine or high-dose oral mesalazine, and no clear evidence that higher doses of oral mesalazine were more efficacious than lower doses. In patients with proctitis and proctosigmoiditis, topical mesalazine was the only treatment that was superior to placebo for prevention of relapse. 5-ASAs were safe and well-tolerated, regardless of treatment regimen.

We used rigorous methodology to maximize the likelihood of identifying all pertinent literature, and to minimize bias. The literature search, eligibility assessment, and data extraction for this network meta-analysis were undertaken independently by multiple reviewers, with any discrepancies resolved by consensus. We used an intention-to-treat analysis, with all dropouts assumed to have failed therapy, and pooled data with a random effects model, to reduce the likelihood that any beneficial effect of oral, topical, or combined oral and topical 5-ASAs has been overestimated. The network meta-analysis allowed us to make indirect comparisons between over 4,000 patients across various dose regimens and drug delivery methods in some of our analyses.

Furthermore, we conducted subgroup analyses to assess treatment efficacy according to disease distribution.

There are some limitations of this study. Our conclusions are limited by the quality of the included trials; only eight were low risk of bias across all domains. Therefore, the results of the network meta-analysis should be interpreted with caution. It is well known that trials that do not report their methodology in sufficient detail tend to overestimate the efficacy of the active intervention studied.[94] Moreover, a wide range of measures of treatment efficacy were used, and they were reported at various timepoints in the studies. However, we tried to standardize this as much as possible in our analyses, according to the criteria used to define remission. There was moderate to high heterogeneity in some of our analyses and evidence of funnel plot asymmetry in some of our analyses. A combination of differences in disease extent among patients recruited into these trials, as well as variations in the specific interventions studied, may have contributed to this. One of the core assumptions in network meta-analysis relates to transitivity, where indirect comparisons between treatments are based on the assumption that any patient included in the network could, theoretically, have been recruited to any of the trials and assigned to any of the treatments. These comparisons are not protected by randomization, and therefore confounding due to underlying differences between RCTs, including patient characteristics, disease distribution and severity, and changes in the natural history of UC over the 30-year range these trials were conducted over, is possible. One final criticism that could be levelled at this study is that the majority of included RCTs were performed in Europe and North America, meaning that the results may not apply to patients with UC in other regions.

We are aware of one other network meta-analysis examining a similar issue,[13] which included 48 trials of induction of remission, and 28 prevention of relapse RCTs, but only in patients with left-sided or extensive UC. This also encompassed trials of olsalazine, sulfasalazine, and budesonide MMX. The authors reported that combined oral and topical 5-ASAs and high-dose oral mesalazine were ranked first and second for induction of remission and were superior to standard

dose oral 5-ASAs. There were no differences between active therapies in terms of prevention of relapse; all were superior to placebo. However, the doses of 5-ASA assigned to low (<2g/day), standard (2g to 3g/day), or high-dose (>3g/day) 5-ASAs were different to the ones we chose, and did not differ according to whether balsalazide or mesalazine was used, and they only considered clinical or endoscopic remission in their analysis, not the more stringent endpoint of clinical and endoscopic remission. Finally, there was no analysis of trials recruiting patients with proctosigmoiditis.

Current guidelines from ECCO recommend topical 5-ASAs for active proctitis, and combined therapy with both oral and topical 5-ASAs for mildly to moderately active left-sided or extensive colitis.[11] Our results support the efficacy of topical mesalazine for proctitis and proctosigmoiditis; it was ranked first or second in most analyses relating to failure to achieve induction of remission when including trials in which ≥50% of patients had disease confined to the rectum and sigmoid. It was superior to both high-dose (≥3.3g/day) and standard-dose (1.7g to 3.2g/day) oral mesalazine for clinical and endoscopic remission combined, and clinical remission, and was superior to standard-dose oral mesalazine for endoscopic remission. Recent guidelines from the American Gastroenterology Association (AGA) suggest that combination therapy is preferable for mildly to moderately active left-sided or extensive disease,[12,95] with oral 5-ASAs given at doses >2 g/day, and at least 1g/day of topical therapy.[95] Although combined oral and topical mesalazine ranked first or second for failure to achieve induction of remission analyses in all trials, and when trials recruiting ≥50% of patients with left-sided or extensive colitis were considered, there were small numbers of RCTs, and patients, included and 95% CIs were wide. In most of our analyses for failure to achieve induction of remission, there were more trials, and more patients, receiving high-dose oral mesalazine. Therefore, evidence to support superiority of combination therapy over high-dose oral mesalazine in left-sided or extensive disease is limited.

Alternatively, the AGA guideline suggests that extensive UC of mild-to-moderate activity can also be managed with standard-dose oral mesalazine (2g to 3g/day) or a diazo-bonded 5-ASA,

such as balsalazide or olsalazine, to induce remission.[12,95] These recommendations were made on the basis of equivalence, in terms of efficacy and safety, between oral doses of 5-ASAs of 2g to 2.4g/day and higher doses of 4.8g/day.[96] However, Hanauer *et al.* reported statistically significant higher rates of mucosal healing and endoscopic improvement, during a 6-week treatment period, with 4.8 g/day oral mesalazine, when compared with a 2.4 g/day regimen, in patients with mildly to moderately active UC.[51,56] Similarly, our network meta-analysis, which included the aforementioned studies, demonstrated that, although high-dose oral mesalazine was ranked lower than combination therapy, it was significantly more efficacious than standard-dose oral mesalazine for a combination of clinical and endoscopic remission, the most stringent endpoint we studied. Sixteen of the 20 RCTs of high-dose oral mesalazine included in this network meta-analysis used doses of 4g/day or higher. Given the absence of dose-dependent toxicity and the potential risks of suboptimal disease control with lower doses of oral mesalazine, on the basis of the results of this network meta-analysis doses of oral mesalazine of 4g/day or higher should be preferred, particularly in patients at high risk of treatment failure. This both supports and informs the recommendations of the AGA guideline concerning the latter group, which includes those with moderate disease naïve to 5-ASAs, those with a suboptimal response to standard-dose mesalazine, and those who require glucocorticosteroids to achieve remission.[95]

Regarding relapse of disease activity, the ECCO guideline states that topical mesalazine should be used as first-line maintenance in proctitis and is an alternative in left-sided colitis.[11] They also recommend that a combination of oral and topical mesalazine be used as second-line maintenance treatment. They propose that effective doses to maintain remission are 2g/day for oral mesalazine and 3g/week in divided doses for topical treatment.[11] Our results demonstrate that although combined oral and topical mesalazine and high-dose oral mesalazine ranked first and second in terms of relapse of disease activity in quiescent UC, most included trials used standard or low-dose oral mesalazine. Standard-dose oral mesalazine trials all used doses of 2.4g/day or more. The added benefits of high-dose mesalazine to prevent relapse of disease activity are unclear. De-

escalation should be considered,[95] but this needs to be done with caution, particularly in patients with a short history of remission, or prior glucocorticosteroid use.[97] When only RCTs recruiting ≥50% of patients with proctitis or proctosigmoiditis were considered, topical mesalazine was the only treatment more efficacious than placebo.

Various diverse mechanisms by which 5-ASAs work in UC have been proposed.[98] However, studies have shown consistently that these drugs appear to induce anti-inflammatory responses by acting locally on the colonic mucosa, rather than systemically. Frieri *et al.* demonstrated that mesalazine concentrations in the rectal and colonic mucosa were significantly higher when combination therapy was administered to patients with UC, compared with oral mesalazine alone.[99] It is therefore intuitive that use of 5-ASAs should aim to maximize coverage of actively inflamed colonic mucosa. However, although combination regimens consisting of both oral and topical mesalazine can be considered in patients with more extensive disease, this network meta-analysis underlines the limited data for their efficacy, versus the alternatives. Higher doses of oral mesalazine may be sufficient, and perhaps more acceptable to patients, as some investigators have shown that adherence to topical therapies is significantly lower than oral 5-ASAs,[100] and foam enemas, in particular, may be poorly tolerated.[101] Despite the fact that, in general, many patients tolerate 5-ASA formulations well, side effects including nausea, abdominal pain, headache, rash, arthralgia, myalgia, or renal impairment may occur.[102] However, in both induction of remission and prevention of relapse trials, total adverse events were no more common with active therapies compared with placebo in this network meta-analysis, and in induction of remission trials withdrawal of therapy due to adverse events was significantly less likely with high-dose and standard-dose oral mesalazine and with standard-dose balsalazide, compared with placebo.

In summary, our network meta-analysis supports recommendations that combined oral and topical 5-ASAs be preferred for induction of remission in mild to moderately active left-sided or extensive UC, and that topical therapies be preferred in proctitis and proctosigmoiditis.[11,12,95] However, higher doses of oral mesalazine (≥3.3g/day) had more evidence for their efficacy than

combined therapy in left-sided or extensive disease and were significantly more efficacious than lower doses. In fact, most trials of high-dose oral mesalazine used doses ≥4g/day. It would appear, therefore, that current recommended doses of oral 5-ASAs for induction of remission are not those likely to be the most efficacious.[12,95] In terms of relapse of disease activity in quiescent UC, topical mesalazine appeared best for disease confined to the rectum or sigmoid, and combined oral and topical mesalazine for left-sided or extensive disease, but there were more trials of oral mesalazine. High-dose oral mesalazine was ranked higher than standard or low-dose, although there was little evidence for difference in efficacy between them. Future RCTs should aim to better establish the role of combined oral and topical therapy for induction of remission in left-sided or extensive UC, as well as examine whether higher doses of oral 5-ASAs are superior in preventing relapse of quiescent disease.

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REFERENCES

1. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohn's Colitis 2017;11:649–670.
2. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1–s106.
3. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12:720–727.
4. Svartz N. Ett nytt sulfonamidpreparat. Forelopande meddelande. Nord Med 1941;9:544.
5. Das KM, Eastwood MA, McManus JPA, et al. Adverse Reactions during Salicylazosulfapyridine Therapy and the Relation with Drug Metabolism and Acetylator Phenotype. N Engl J Med 1973;289:491–495.
6. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis. N Engl J Med 1987;317:1625–1629.
7. Fumery M, Singh S, Dulai PS, et al. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol 2018;16:343-356.e3.
8. Ford AC, Khan KJ, Achkar JP, et al. Efficacy of oral vs. Topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: Systematic review and meta-analysis. Am J Gastroenterol 2012;107:167–176.
9. Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of Topical 5-Aminosalicylates in Preventing Relapse of Quiescent Ulcerative Colitis: A Meta-analysis. Clin Gastroenterol Hepatol 2012;10:513–519.
10. Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of

remission in ulcerative colitis. Cochrane Database Syst Rev 2010.

11. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. J Crohn's Colitis 2017;11:769–784.
12. Ko CW, Singh S, Feuerstein JD, et al. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology 2019;156:748–764.
13. Nguyen NH, Fumery M, Dulai PS, et al. Comparative efficacy and tolerability of pharmacological agents for management of mild to moderate ulcerative colitis: a systematic review and network meta-analyses. Lancet Gastroenterol Hepatol 2018;3:742–753.
14. Laasila K, Leirisalo-Repo M. Side effects of sulphasalazine in patients with rheumatic diseases or inflammatory bowel disease. Scand J Rheumatol 1994;23:338–340.
15. Parry SD, Barbatzas C, Peel ET, et al. Sulphasalazien and lung toxicity. Eur Respir J 2002;19:756–764.
16. Kruis W, Schreiber S, Theuer D, et al. Low dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3.0 g twice daily) was superior in preventing relapses. Gut 2001;49:783–789.
17. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 2011. https://handbook-5-1.cochrane.org/ (accessed June 29, 2019). Gastroenterol Hepatol 19.
18. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann Intern Med 2015;162:777–784.
19. Salanti G, Higgins JPT, Ades AE, et al. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17:279–301.
20. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence

synthesis tool. Res Synth Methods 2012;3:80–97.

21. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. J Clin Epidemiol 2011;64:163–171.
22. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:1–8.
23. Chaimani A, Higgins JPT, Mavridis D, et al. Graphical Tools for Network Meta-Analysis in STATA Haibe-Kains B, ed. PLoS One 2013;8:e76654.
24. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–560.
25. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15.
26. Morton SC, Murad MH, O'Connor E et al. Quantitative Synthesis—An Update. In Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality (US) 2018.
27. Powell-Tuck J, MacRAE KD, Parkins RA, et al. A defence of the small clinical trial: Evaluation of three gastroenterological studies. Br Med J (Clin Res Ed) 1986;292:599–602.
28. Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic Acid Enema in the Treatment of Distal Ulcerative Colitis, Proctosigmoiditis, and Proctitis. Gastroenterology 1987;92:1894-1898.
29. Sandborn WJ, Hanauer S, Lichtenstein GR, et al. Early symptomatic response and mucosal healing with mesalazine rectal suspension therapy in active distal ulcerative colitis - Additional results from two controlled studies. Aliment Pharmacol Ther 2011;34:747–756.
30. William CN, Haber G, Aquino JA. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using99mTc-

labeled 5-ASA suppositories. Dig Dis Sci 1987;32.

31. Riley SA, Mani V, Goodman MJ, et al. Comparison of delayed release 5 aminosalicyclic acid (mesazaline) and sulphalazine in the treatment of mild to moderate ulcerative colitis relapse. Gut 1988;29:669–674.

32. Campieri M, Gionchetti P, Belluzzi A, et al. Topical treatment with 5-aminosalicylic in distal ulcerative colitis by using a new suppository preparation - A double-blind placebo controlled trial. Int J Colorectal Dis 1990;5:79–81.

33. Campieri M, De Franchis R, Bianchi Porro G, et al. Mesalazine (5-aminosalicylic acid) suppositories in the treatment of ulcerative proctitis or distal proctosigmoiditis: A randomized controlled trial. Scand J Gastroenterol 1990;25:663–668.

34. Miglioli M, Bianchi Porro G, Brunetti G, Sturniolo GC. Delayed-release mesalazine in the treatment of nild ulcerative colitis: a dose ranging study. Eur J Gastroenterol Hepatol 1990;2:229–234.

35. Massimo Campieri, Paolo Gionchetti AB et al. Sucralfate, 5-aminosalicylic acid and placebo enemas in the treatment of distal ulcerative colitis. Eur J Gastroenterol Hepatol 1991;3:41–44.

36. Campieri M, Gionchetti P, Belluzzi A, et al. Optimum dosage of 5-Aminosalicylic acid as rectal enemas in patients with active ulcerative colitis. Gut 1991;32:929–931.

37. Miner P, Nostrant T WL. Multicenter trial of Pentasa for active ulcerative colitis. Intest Disord 1991;A231.

38. Sninsky CA, Cort DH, Shanahan F, et al. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis: A multicenter study. In: *Annals of Internal Medicine*.Vol 115. Ann Intern Med; 1991:350–355.

39. Hanauer S, Schwartz J, Robinson M, et al. Mesalamine Capsules for Treatment of Active Ulcerative Colitis: Results of a Controlled Trial. Pentasa Study Group. The American Journal of Gastroenterology. 1993;88.8:1188-1197.

40. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol 1997;92:1867–1871.

41. Gionchetti P, Rizzello F, Venturi A, et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. Dis Colon Rectum 1998;41:93–97.

42. Green JRB, Lobo AJ, Holdsworth CD, et al. Balsalazide Is More Effective and Better Tolerated Than Mesalamine in the Treatment of Acute Ulcerative Colitis. Gastroenterology. 1998;114:15-22.

43. Hanauer SB (For The U.S PENTASA Enema Study Group). Dose-Ranging Study of Mesalamine (PENTASA) Enemas in the Treatment of Acute Ulcerative Proctosigmoiditis: Results of a Multicentered Placebo-Controlled Trial. Inflamm Bowel Dis 1998;4:79–83.

44. Pokrotnieks, Marlicz, Paradowski, et al. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: A double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther 2000;14:1191–1198.

45. Vecchi M, Meucci G, Gionchetti P, et al. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. Aliment Pharmacol Ther 2001;15:251–256.

46. Levine DS, Riff DS, Pruitt R, et al. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis1. Am J Gastroenterol 2002;97:1398–1407.

47. Malchow H, Gertz B. A new mesalazine foam enema (Claversal Foam) compared with a standard liquid enema in patients with active distal ulcerative colitis. Aliment Pharmacol Ther 2002;16:415–423.

48. Pruitt R, Hanson J, Safdi M, et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. Am J Gastroenterol 2002;97:3078–3086.

49. Kruis W, Bar-Meir S, Feher J, et al. The optimal dose of 5-aminosalicylic acid in active ulcerative colitis: A dose-finding study with newly developed mesalamine. Clin Gastroenterol Hepatol 2003;1:36–43.

50. Tursi A, Brandimarte G, Giorgetti GM, et al. Low-dose Balsalazide Plus a High-Potency Probiotic Preparation Is More Effective Than Balsalazide Alone or Mesalazine in the Treatment of Acute Mild-To-Moderate Ulcerative Colitis. Med Sci Monit. 2004;10.11:126-131.

51. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: The ASCEND II trial. Am J Gastroenterol 2005;100:2478–2485.

52. Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: A randomised, double blind, placebo controlled study. Gut 2005;54:960–965.

53. Probert CSJ, Dignass AU, Lindgren S, et al. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: Rapid symptom resolution and improvements in quality of life. J Crohn's Colitis 2014;8:200–207.

54. Prantera C, Viscido A, Biancone L, et al. A new oral delivery system for 5-ASA: Preliminary clinical findings for MMx. Inflamm Bowel Dis 2005;11:421–427.

55. D'Haens G, Hommes D, Engels L, et al. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: A phase II, dose-ranging study. Aliment Pharmacol Ther 2006;24:1087–1097.

56. Hanauer SB, William J Sandborn, Dallaire C, et al. Delayed-release Oral Mesalamine 4.8 g/day (800 Mg Tablets) Compared to 2.4 g/day (400 Mg Tablets) for the Treatment of Mildly to Moderately Active Ulcerative Colitis: The ASCEND I Trial. Can J Gastroenterol 2007;21.

57. Kamm MA, Sandborn WJ, Gassull M, et al. Once-Daily, High-Concentration MMX

Mesalamine in Active Ulcerative Colitis. Gastroenterology 2007;132:66–75.

58. Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of Once- or Twice-Daily MMX Mesalamine (SPD476) for the Induction of Remission of Mild to Moderately Active Ulcerative Colitis. Clin Gastroenterol Hepatol 2007;5:95–102.

59. Sandborn WJ, Regula J, Feagan BG, et al. Delayed-Release Oral Mesalamine 4.8 g/day (800-mg Tablet) Is Effective for Patients With Moderately Active Ulcerative Colitis. Gastroenterology 2009.

60. Scherl EJ, Pruitt R, Gordon GL, et al. Safety and efficacy of a new 3.3g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: A multicenter, randomized, double-blind, placebo-controlled study. Am J Gastroenterol 2009;104:1452–1459.

61. Andus T, Kocjan A, Müser M, et al. Clinical trial: A novel high-dose 1 g mesalamine suppository (salofalk) once daily is as efficacious as a 500-mg suppository thrice daily in active ulcerative proctitis. Inflamm Bowel Dis 2010;16:1947–1956.

62. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: A double-blind, randomized study. Inflamm Bowel Dis 2010;16:1575–1582.

63. Hiwatashi N, Suzuki Y, Mitsuyama K, et al. Clinical trial: Effects of an oral preparation of mesalazine at 4 g/day on moderately active ulcerative colitis. A phase III parallel-dosing study. J Gastroenterol 2011;46:46–56.

64. Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: Results from the CORE i study. Gastroenterology 2012;143.

65. Feagan BG, Sandborn WJ, D'Haens G, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology 2013;145.

66. Watanabe M, Nishino H, Sameshima Y, et al. Randomised clinical trial: Evaluation of the efficacy of mesalazine (mesalamine) suppositories in patients with ulcerative colitis and active rectal inflammation - A placebo-controlled study. Aliment Pharmacol Ther 2013;38:264–273.

67. Pontes C, Vives R, Torres F, et al. Safety and activity of dersalazine sodium in patients with mild-to-moderate active colitis: Double-blind randomized proof of concept study. Inflamm Bowel Dis 2014;20:2004–2012.

68. Kato S, Kani K, Kurihara H, et al. Comparison of Rectal With Oral Mesalazine in the Treatment of Rectal Ulcerative Proctitis (CORRECT Study). Gastroenterology 2016;150:S775.

69. Ogata H, Yokoyama T, Mizushima S, et al. Comparison of efficacy of once daily multimatrix mesalazine 2.4 g/day and 4.8 g/day with other 5-aminosalicylic acid preparation in active ulcerative colitis: A randomized, double-blind study. Intest Res 2018;16:255–266.

70. Ye LN. Combined oral and suppository treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with mild/moderate extensive or left-sided active ulcerative colitis: A randomized multi-center controlled study. Journal of Digestive Disease. 2018:19(Supp 1):35.

71. Sutherland LR, Martin F. 5-Aminosalicylic Acid Enemas in the Maintenance of Remission in Distal Ulcerative Colitis and Proctitis. The Canadian Journal of Gastroenterology. 1987;1.1:3-6.

72. Biddle WL, Greenberger NJ, Swan JT, et al. 5-Aminosalicylic acid enemas: Effective agent in maintaining remission in left-sided ulcerative colitis. Gastroenterology 1988;94:1075–1079.

73. D'Arienzo A, Panarese A DF et al. 5-Aminosalicylic Acid Suppositories in the Maintenance of Remission in Idiopathic Proctitis or Proctosigmoiditis: A Double-Blind Placebo-Controlled Clinical Trial - PubMed. Am J Gastroenterol 1990;85.

74. Green JRB, Swan CHJ, Rowlinson A, et al. Short report: comparison of two doses of balsalazide in maintaining ulcerative colitis in remission over 12 months. Alimentary Pharmacology &Therapeutics. 1992;6:647-652.

75. Mantzaris GJ, Hatzis A, Petraki K, et al. Intermittent therapy with high-dose 5-aminosalicylic acid enemas maintains remission in ulcerative proctitis and proctosigmoiditis. Dis Colon Rectum 1994;37:58–62.

76. Miner P, Daly T, Nester T and The Rowasa Study Group. The effect of varying dose intervals of mesalamine enemas for the prevention of relapse in distal ulcerative colitis. 1994.

77. Fockens P, Mulder CJJ, Tytgat GNJ, et al. Comparison of the efficacy and safety of 1.5 compared with 3.0 g oral slow-release mesalazine (pentasa) in the maintenance treatment of ulcerative colitis. Eur J Gastroenterol Hepatol 1995;7:1025–1030.

78. Miner P, Hanauer S, Robinson M, et al. Safety and efficacy of controlled-release mesalamine for maintenance of remission in ulcerative colitis. Dig Dis Sci 1995;40:296–304.

79. Hanauer SB, Sninsky CA, Robinson M, et al. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis. A randomized, placebo-controlled trial. Ann Intern Med 1996;124:204–211.

80. D'Albasio G, Pacini F CE et al. Combined Therapy With 5-aminosalicylic Acid Tablets and Enemas for Maintaining Remission in Ulcerative Colitis: A Randomized Double-Blind Study. Am J Gastroenterol 1997;92.

81. Hawkey CJ, Dube LM, Rountree L V., et al. A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. Gastroenterology 1997;112:718–724.

82. D'Albasio G, Paoluzi P, Campieri M, et al. Maintenance treatment of ulcerative proctitis with mesalazine suppositories: a double-blind placebo-controlled trial. Am J Gastroenterol 1998;93:799–803.

83. Green JRB, Gibson JA, Kerr GD, et al. Maintenance of remission of ulcerative colitis: A comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months.

Aliment Pharmacol Ther 1998;12:1207–1216.

84. Marteau P, Grand J, Foucault M, et al. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: A randomised double blind placebo controlled multicentre study. Gut 1998;42:195–199.

85. Ardizzone S, Petrillo M, Imbesi V, et al. Is maintenance therapy always necessary for patients with ulcerative colitis in remission? Aliment Pharmacol Ther 1999;13:373–379.

86. Hanauer S, Good LI, Goodman MW, et al. Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. Am J Gastroenterol 2000;95:1749–1754.

87. Paoluzi OA, Iacopini F, Pica R, et al. Comparison of two different daily dosages (2.4 vs. 1.2 g) of oral mesalazine in maintenance of remission in ulcerative colitis patients: 1-Year follow-up study. Aliment Pharmacol Ther 2005;21:1111–1119.

88. Yokoyama H, Takagi S, Kuriyama S, et al. Effect of weekend 5-aminosalicylic acid (mesalazine) enema as maintenance therapy for ulcerative colitis: Results from a randomized controlled study. Inflamm Bowel Dis 2007;13:1115–1120.

89. Lichtenstein GR, Gordon GL, Zakko S, et al. Clinical trial: Once-daily mesalamine granules for maintenance of remission of ulcerative colitis - A 6-month placebo-controlled trial. Aliment Pharmacol Ther 2010;32:990–999.

90. Kruis W, Jonaitis L, Pokrotnieks J, et al. Randomised clinical trial: A comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. Aliment Pharmacol Ther 2011;33:313–322.

91. D'Haens G, Sandborn WJ, Barrett K, et al. Once-Daily MMX® Mesalamine for Endoscopic Maintenance of Remission of Ulcerative Colitis. Am J Gastroenterol 2012;107:1064–1077.

92. Pica R, Cassieri C, Cocco A, et al. A randomized trial comparing 4.8 vs. 2.4g/day of oral mesalazine for maintenance of remission in ulcerative colitis. Dig Liver Dis 2015;47:933–937.

93. Gordon GL, Zakko S, Murthy U, et al. Once-daily mesalamine formulation for maintenance of remission in ulcerative colitis. J Clin Gastroenterol 2016;50:318–325.

94. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. Br Med J 2001;323:42–46.

95. Singh S, Feuerstein JD, Binion DG, et al. AGA Technical Review on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology 2019;156:769-808.e29.

96. Wang Y, Parker CE, Bhanji T, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2016;2016.

97. Fukuda T, Naganuma M, Sugimoto S, et al. The risk factor of clinical relapse in ulcerative colitis patients with low dose 5-aminosalicylic acid as maintenance therapy: A report from the IBD registry. PLoS One 2017;12.

98. Punchard NA, Greenfield SM, Thompson RPH. Mechanism of Action of 5-Aminosalicylic Acid. Mediators Inflamm 1992;1:151–165.

99. Frieri G, Pimpo MT, Palumbo GC, et al. Rectal and colonic mesalazine concentration in ulcerative colitis: Oral vs. oral plus topical treatment. Aliment Pharmacol Ther 1999;13:1413–1417.

100. D'Incà R, Bertomoro P, Mazzocco K, et al. Risk factors for non-adherence to medication in inflammatory bowel disease patients. Aliment Pharmacol Ther 2008;27:166–172.

101. Gionchetti P, Ardizzone S, Benvenuti ME, et al. A new mesalazine gel enema in the treatment of left-sided ulcerative colitis: A randomized controlled multicentre trial. Aliment Pharmacol Ther 1999;13:381–388.

102. Ham M, Moss AC. Mesalamine in the treatment and maintenance of remission of ulcerative colitis. Expert Rev Clin Pharmacol 2012;5:113–123.

FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Network Meta-analysis.

Figure 2. Network Meta-analysis of Likelihood of Failure to Achieve Clinical and Endoscopic Remission in Induction of Remission Trials.

A. **Forest Plot for Failure to Achieve Clinical and Endoscopic Remission in Induction of Remission Trials.**
B. **Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Clinical and Endoscopic Remission in Induction of Remission Trials.**

Figure 3. Network Meta-analysis of Likelihood of Failure to Achieve Clinical Remission in Induction of Remission Trials.

A. **Forest Plot for Failure to Achieve Clinical Remission in Induction of Remission Trials.**
B. **Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Clinical Remission in Induction of Remission Trials.**

Figure 4. Network Meta-analysis of Likelihood of Failure to Achieve Endoscopic Remission in Induction of Remission Trials.

A. **Forest Plot for Failure to Achieve Endoscopic Remission in Induction of Remission Trials.**
B. **Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Endoscopic Remission in Induction of Remission Trials.**

Figure 5. Network Meta-analysis of Likelihood of Relapse of Disease Activity in Prevention of Relapse Trials.

A. **Forest Plot for Relapse of Disease Activity in Prevention of Relapse Trials.**
B. **Summary Treatment Effects from the Network Meta-analysis for Relapse of Disease Activity in Prevention of Relapse Trials.**

Figure 1. Flow Diagram of Assessment of Studies Identified in the Network Meta-analysis.

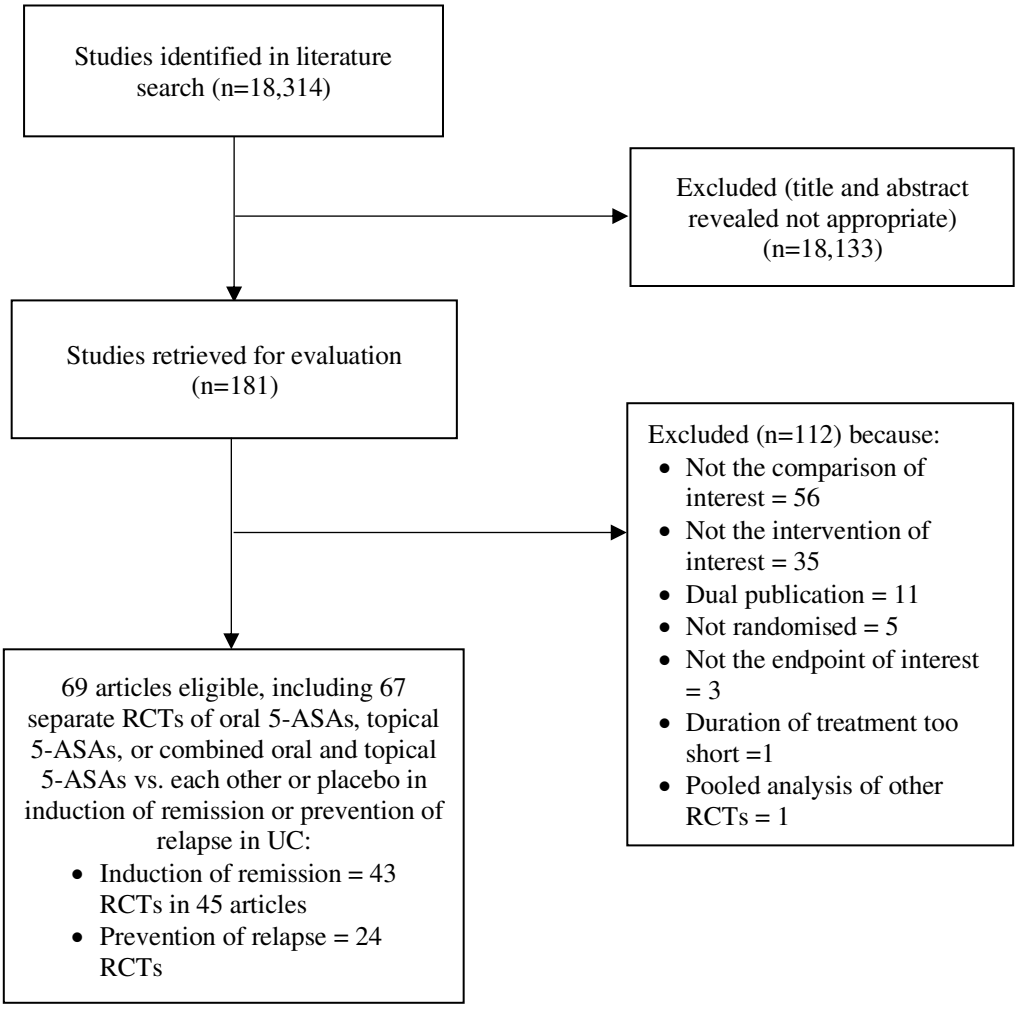
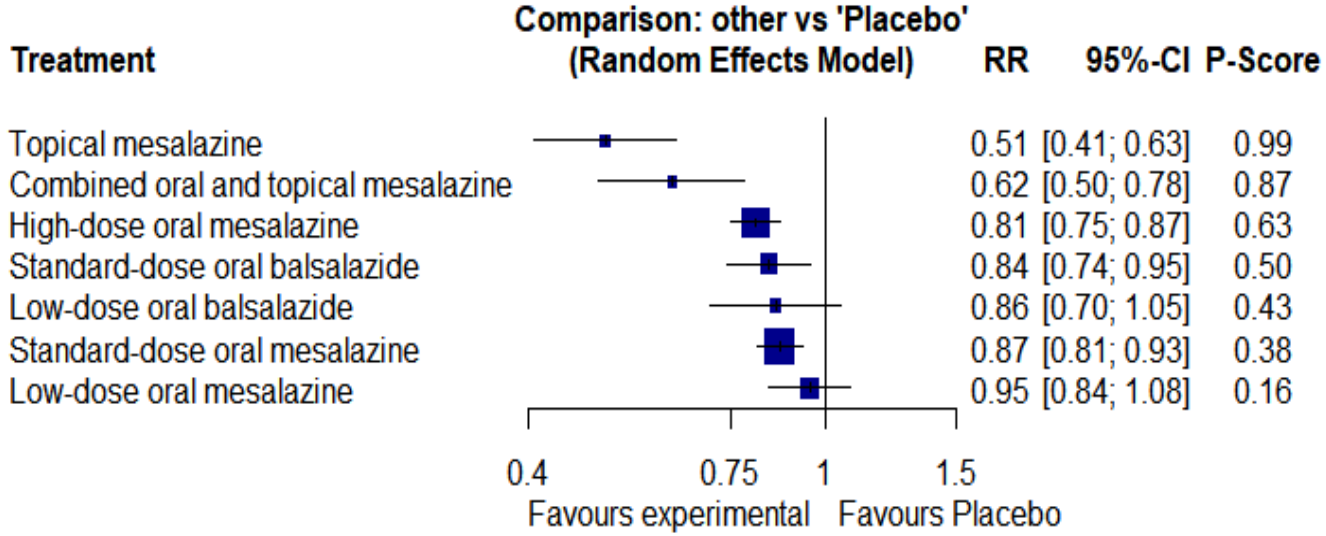


Figure 2. Network Meta-analysis of Likelihood of Failure to Achieve Clinical and Endoscopic Remission in Induction of Remission Trials.

A. Forest Plot for Failure to Achieve Clinical and Endoscopic Remission in Induction of Remission Trials.



Note: Treatments are reported in order of efficacy ranking according to P-score.

The P-score is the probability of each treatment being ranked as best in terms of efficacy in the network.

B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Clinical and Endoscopic Remission in Induction of Remission Trials.

Topical mesalazine	**1.85 [0.83; 4.12]**	**N/A**	**N/A**	**N/A**	**0.81 [0.48; 1.37]**	**N/A**	**0.46 [0.36; 0.59]**
0.81 [0.60; 1.11]	**Combined oral and topical mesalazine**	**0.82 [0.66; 1.02]**	**N/A**	**N/A**	**0.44 [0.21; 0.92]**	**N/A**	**N/A**
0.63 [0.50; 0.79]	**0.77 [0.63; 0.96]**	**High-dose oral mesalazine**	**N/A**	**N/A**	**0.94 [0.88; 1.02]**	**0.83 [0.67; 1.03]**	**0.79 [0.71; 0.87]**
0.60 [0.47; 0.78]	**0.74 [0.58; 0.95]**	**0.96 [0.84; 1.10]**	**Standard-dose oral balsalazide**	**0.99 [0.80; 1.22]**	**0.91 [0.77; 1.06]**	**N/A**	**0.92 [0.76; 1.10]**
0.59 [0.44; 0.80]	**0.73 [0.54; 0.97]**	**0.94 [0.77; 1.15]**	**0.98 [0.81; 1.19]**	**Low-dose oral balsalazide**	**1.00 [0.81; 1.23]**	**N/A**	**N/A**
0.58 [0.47; 0.73]	**0.72 [0.58; 0.90]**	**0.93 [0.87; 0.99]**	**0.97 [0.86; 1.09]**	**0.99 [0.81; 1.20]**	**Standard-dose oral mesalazine**	**0.92 [0.78; 1.10]**	**0.87 [0.80; 0.94]**
0.53 [0.41; 0.69]	**0.65 [0.51; 0.84]**	**0.85 [0.74; 0.96]**	**0.88 [0.75; 1.04]**	**0.90 [0.72; 1.13]**	**0.91 [0.81; 1.03]**	**Low-dose oral mesalazine**	**0.94 [0.81; 1.08]**
0.51 [0.41; 0.63]	**0.62 [0.50; 0.78]**	**0.81 [0.75; 0.87]**	**0.84 [0.74; 0.95]**	**0.86 [0.70; 1.05]**	**0.87 [0.81; 0.93]**	**0.95 [0.84; 1.08]**	**Placebo**

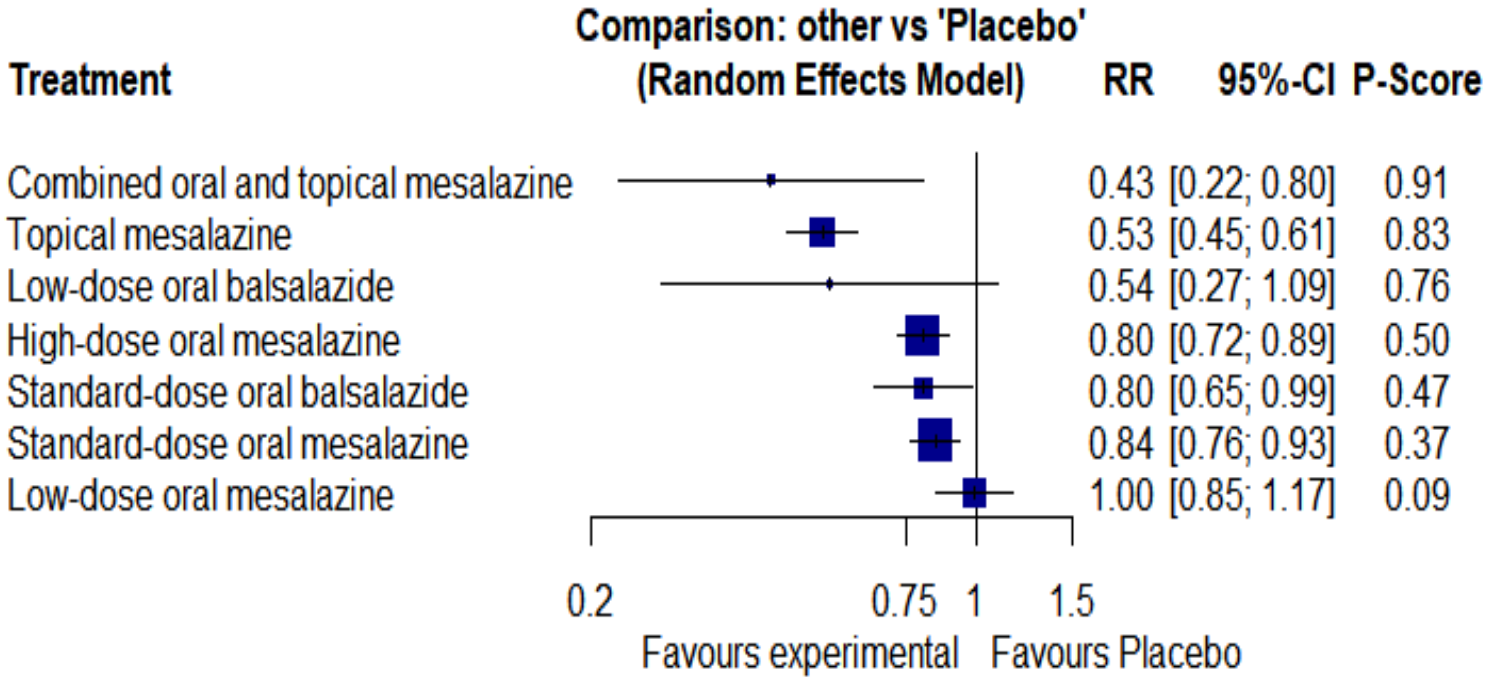
League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve clinical and endoscopic remission in induction of remission trials. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of

direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons.

Figure 3. Network Meta-analysis of Likelihood of Failure to Achieve Clinical Remission in Induction of Remission Trials.

A. Forest Plot for Failure to Achieve Clinical Remission in Induction of Remission Trials.



Note: Treatments are reported in order of efficacy ranking according to P-score.

The P-score is the probability of each treatment being ranked as best in terms of efficacy in the network.

B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Clinical Remission in Induction of Remission Trials.

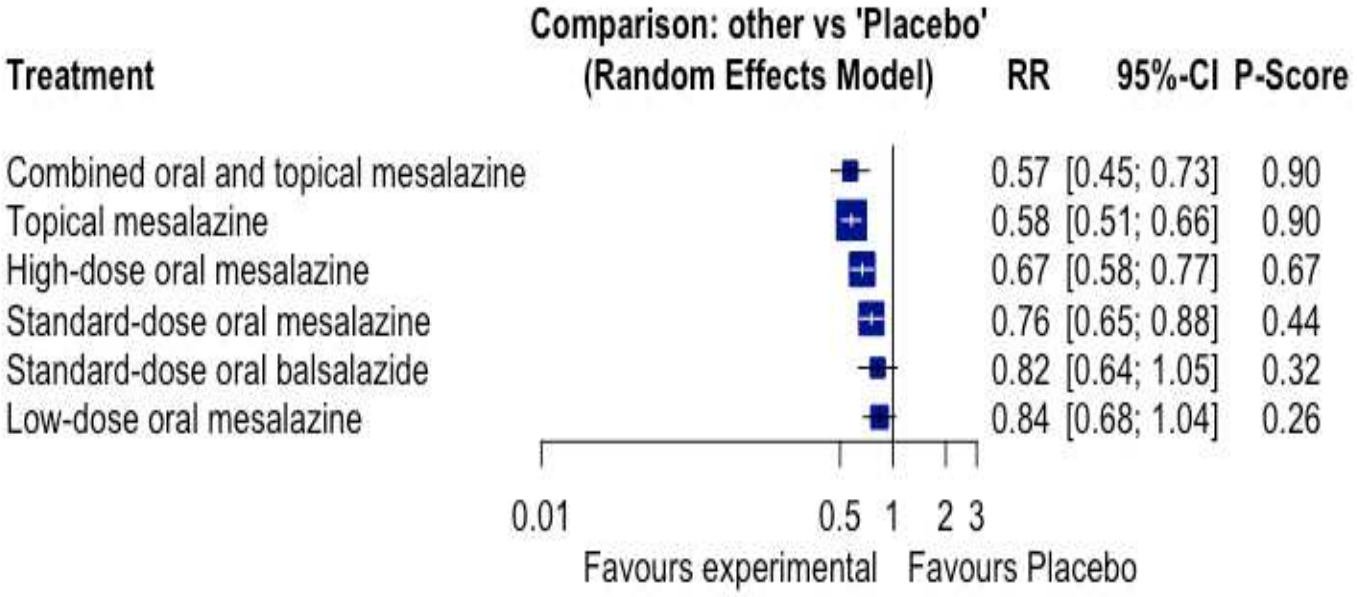
Combined oral and topical mesalazine	**0.51 [0.18; 1.50]**	**N/A**	**0.71 [0.30; 1.66]**	**N/A**	**0.37 [0.14; 0.97]**	**N/A**	**N/A**
0.81 [0.42; 1.54]	**Topical mesalazine**	**N/A**	**0.92 [0.58; 1.45]**	**N/A**	**0.48 [0.26; 0.87]**	**N/A**	**0.51 [0.44; 0.60]**
0.78 [0.31; 2.01]	**0.97 [0.47; 1.99]**	**Low-dose oral balsalazide**	**N/A**	**N/A**	**0.64 [0.32; 1.29]**	**N/A**	**N/A**
0.53 [0.28; 1.00]	**0.66 [0.55; 0.78]**	**0.68 [0.34; 1.37]**	**High-dose oral mesalazine**	**N/A**	**0.96 [0.86; 1.08]**	**0.85 [0.70; 1.02]**	**0.82 [0.72; 0.93]**
0.53 [0.27; 1.03]	**0.66 [0.51; 0.84]**	**0.68 [0.33; 1.40]**	**1.00 [0.80; 1.25]**	**Standard-dose oral balsalazide**	**0.96 [0.69; 1.33]**	**N/A**	**0.80 [0.62; 1.03]**
0.50 [0.27; 0.95]	**0.62 [0.53; 0.74]**	**0.64 [0.32; 1.29]**	**0.95 [0.86; 1.05]**	**0.95 [0.77; 1.17]**	**Standard-dose oral mesalazine**	**0.80 [0.67; 0.95]**	**0.84 [0.75; 0.94]**
0.43 [0.22; 0.82]	**0.53 [0.43; 0.65]**	**0.55 [0.27; 1.11]**	**0.80 [0.69; 0.94]**	**0.81 [0.63; 1.04]**	**0.85 [0.73; 0.99]**	**Low-dose oral mesalazine**	**0.90 [0.72; 1.14]**
0.43 [0.22; 0.80]	**0.53 [0.45; 0.61]**	**0.54 [0.27; 1.09]**	**0.80 [0.72; 0.89]**	**0.80 [0.65; 0.99]**	**0.84 [0.76; 0.93]**	**1.00 [0.85; 1.17]**	**Placebo**

League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve clinical remission in induction of remission trials. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons.

Figure 4. Network Meta-analysis of Likelihood of Failure to Achieve Endoscopic Remission in Induction of Remission Trials.

A. Forest Plot for Failure to Achieve Endoscopic Remission in Induction of Remission Trials.



Note: Treatments are reported in order of efficacy ranking according to P-score.

The P-score is the probability of each treatment being ranked as best in terms of efficacy in the network.

B. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Endoscopic Remission in Induction of Remission Trials.

Combined oral and topical mesalazine	**1.04 [0.67; 1.62]**	**0.78 [0.60; 1.02]**	**0.97 [0.65; 1.46]**	**N/A**	**N/A**	**N/A**
0.98 [0.76; 1.27]	**Topical mesalazine**	**1.17 [0.76; 1.79]**	**0.75 [0.52; 1.07]**	**N/A**	**N/A**	**0.57 [0.50; 0.65]**
0.85 [0.69; 1.07]	**0.87 [0.73; 1.03]**	**High-dose oral mesalazine**	**0.86 [0.74; 1.01]**	**N/A**	**0.82 [0.63; 1.05]**	**0.68 [0.58; 0.81]**
0.76 [0.60; 0.96]	**0.77 [0.65; 0.92]**	**0.89 [0.77; 1.02]**	**Standard-dose oral mesalazine**	**N/A**	**0.91 [0.74; 1.12]**	**0.76 [0.64; 0.92]**
0.70 [0.49; 0.99]	**0.71 [0.54; 0.94]**	**0.82 [0.61; 1.09]**	**0.92 [0.69; 1.23]**	**Standard-dose oral balsalazide**	**N/A**	**0.82 [0.64; 1.05]**
0.68 [0.51; 0.91]	**0.69 [0.55; 0.87]**	**0.80 [0.65; 0.98]**	**0.90 [0.74; 1.09]**	**0.98 [0.70; 1.35]**	**Low-dose oral mesalazine**	**0.87 [0.63; 1.19]**
0.57 [0.45; 0.73]	**0.58 [0.51; 0.66]**	**0.67 [0.58; 0.77]**	**0.76 [0.65; 0.88]**	**0.82 [0.64; 1.05]**	**0.84 [0.68; 1.04]**	**Placebo**

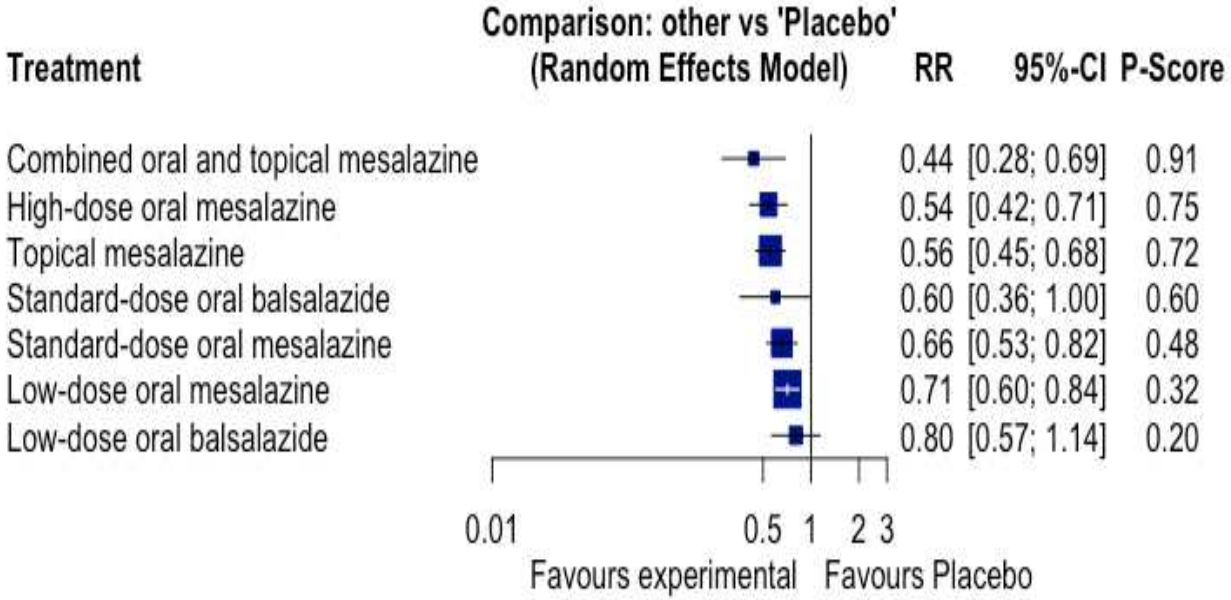
League table of pairwise comparisons in the network meta-analysis for the relative risk of failure to achieve endoscopic remission in induction of remission trials. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and

are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons.

Figure 5. Network Meta-analysis of Likelihood of Relapse of Disease Activity in Prevention of Relapse Trials.

A. Forest Plot for Relapse of Disease Activity in Prevention of Relapse Trials.



Note: Treatments are reported in order of efficacy ranking according to P-score.

The P-score is the probability of each treatment being ranked as best in terms of efficacy in the network.

B. Summary Treatment Effects from the Network Meta-analysis for Relapse of Disease Activity in Prevention of Relapse Trials.

Combined oral and topical mesalazine	**N/A**	**N/A**	**N/A**	**0.24 [0.06; 0.87]**	**0.69 [0.44; 1.08]**	**N/A**	**N/A**
0.81 [0.48; 1.35]	**High-dose oral mesalazine**	**N/A**	**N/A**	**0.70 [0.38; 1.30]**	**N/A**	**N/A**	**0.56 [0.42; 0.75]**
0.79 [0.48; 1.29]	**0.97 [0.70; 1.36]**	**Topical mesalazine**	**N/A**	**N/A**	**0.38 [0.17; 0.89]**	**N/A**	**0.58 [0.47; 0.72]**
0.73 [0.38; 1.38]	**0.90 [0.51; 1.59]**	**0.93 [0.54; 1.60]**	**Standard-dose oral balsalazide**	**N/A**	**0.52 [0.26; 1.05]**	**0.74 [0.49; 1.12]**	**N/A**
0.67 [0.43; 1.04]	**0.83 [0.60; 1.13]**	**0.85 [0.63; 1.14]**	**0.91 [0.55; 1.51]**	**Standard-dose oral mesalazine**	**0.90 [0.77; 1.05]**	**N/A**	**N/A**
0.61 [0.40; 0.94]	**0.76 [0.57; 1.02]**	**0.78 [0.60; 1.01]**	**0.84 [0.52; 1.36]**	**0.92 [0.79; 1.07]**	**Low-dose oral mesalazine**	**0.84 [0.62; 1.15]**	**0.68 [0.57; 0.81]**
0.54 [0.32; 0.92]	**0.67 [0.44; 1.03]**	**0.69 [0.46; 1.03]**	**0.75 [0.50; 1.12]**	**0.82 [0.58; 1.15]**	**0.89 [0.65; 1.20]**	**Low-dose oral balsalazide**	**N/A**
0.44 [0.28; 0.69]	**0.54 [0.42; 0.71]**	**0.56 [0.45; 0.68]**	**0.60 [0.36; 1.00]**	**0.66 [0.53; 0.82]**	**0.71 [0.60; 0.84]**	**0.80 [0.57; 1.14]**	**Placebo**

League table of pairwise comparisons in the network meta-analysis for the relative risk of relapse of disease activity in prevention of relapse trials.

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered

relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes highlighted in light orange indicate significant differences. Direct comparisons are provided above the drug labels, and indirect comparisons are below.

N/A; not applicable, no RCTs making direct comparisons.

Table 1. Eligibility Criteria.

Randomised controlled trials.
Adults (>90% of patients aged >16 years) with ulcerative colitis (UC).
Compared oral, topical, or combined oral and topical 5-ASA drugs* with each other†, or with placebo.
Minimum duration of therapy of 14 days in trials reporting on failure of induction of remission in active UC.
Minimum duration of therapy of 6 months in trials reporting relapse of disease activity in quiescent UC.
Assessment of failure to achieve remission in active UC, or relapse of disease activity in quiescent UC, at last time point of assessment in the trial±.

*Mesalazine or balsalazide.

†For trials that only compared different dosages of oral 5-ASAs with each other, we classified these according to total daily dose. For oral mesalazine this was as follows: ≤1.6g/day low-dose; 1.7g to 3.2g/day standard-dose; ≥3.3g/day high-dose. For oral balsalazide, which has a lower total dose of 5-ASA (1g balsalazide delivers 0.35g 5-ASA)[16] this was as follows: ≤4.5g/day low-dose; ≥4.6g/day standard-dose.

±For trials reporting failure of induction of remission we extracted data for any of the following: clinical and endoscopic remission combined (e.g. as part of a disease activity index, such as the Mayo score); clinical remission; endoscopic remission; or histological remission, wherever reported. For trials of relapse of disease activity, we extracted data for clinical and endoscopic relapse combined, clinical relapse, endoscopic relapse, or histological relapse.