



Original Article

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

Brigida Barberio,^{a*} Jonathan P. Segal,^{b*,e} M. Nabil Quraishi,^{c,d*} Christopher J. Black,^{e,f} Edoardo V. Savarino^{a,g}, Alexander C. Ford,^{e,f}

^aDepartment of Surgery, Oncology and Gastroenterology [DISCOG], Gastroenterology Unit, University of Padova-Azienda Ospedaliera di Padova, Padova, Italy ^bDepartment of Gastroenterology and Hepatology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK ^cDepartment of Gastroenterology, University Hospitals Birmingham, Birmingham, UK ^dUniversity of Birmingham Microbiome Treatment Centre, University of Birmingham, UK ^eLeeds Gastroenterology Institute, St James's University Hospital, Leeds, UK ^fLeeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK

Corresponding author: Professor Alexander C. Ford, MD, Leeds Gastroenterology Institute, Room 125, 4th Floor, Bexley Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK. Tel.: +441132684963; email: alex12399@yahoo.com

*Denotes joint first authors.

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 remain 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 summarise 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 $\geq 50\%$ of patients had left-sided/extensive disease, and topical mesalazine first in trials where $\geq 50\%$ of patients had proctitis/proctosigmoiditis. High-dose [≥ 3.3 g/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.

Podcast: This article has an associated podcast which can be accessed at <https://academic.oup.com/ecco-jcc/pages/podcast>

Key Words: 5-Aminosalicylates; 5-ASAs; inflammatory bowel disease; ulcerative colitis; network; meta-analysis

1. 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 affected 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 sulphasalazine in UC was reported in 1941,⁴ its acceptability in clinical practice has been limited by various side effects, thought to arise from the sulphapyridine moiety, including nausea, vomiting, anaemia, 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 sulphapyridine 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 2 g to 3 g/day] mesalazine or diazo-bonded 5-ASA [eg, balsalazide], to induce remission.¹² Regarding prevention of relapse, current European Crohn's and Colitis Organisation [ECCO] guidelines state that rectal mesalazine should 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; there have been further studies 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, previous 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. An earlier 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 sulphasalazine is limited by tolerability.^{14,15}

2. Methods

2.1. Search strategy and study selection

A search of the medical literature was conducted using MEDLINE [1946 to 2 December 2020], EMBASE and EMBASE classic [1947 to the 2 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 [Box 1]. The first period of cross-over 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 which 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.

2.2. 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.

2.3. 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 ≤ 1.6 g/day as low-dose, 1.7 g to 3.2 g/day as standard-dose, and ≥ 3.3 g/day as high-dose. For oral balsalazide, which has a lower total dose of 5-ASA [1 g balsalazide delivers 0.35 g 5-ASA], this was as follows: ≤ 4.5 g/day as low-dose and ≥ 4.6 g/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 [ie, 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.

2.4. 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.

2.5. 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 summarise the effect of each comparison tested using a random effects model as a conservative estimate. The RR of failure to achieve remission and the 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 $\geq 75\%$ 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 only in trials that recruited $\geq 50\%$ of patients with proctitis or proctosigmoiditis, or only in trials in which $\geq 50\%$ 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.

3. 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}

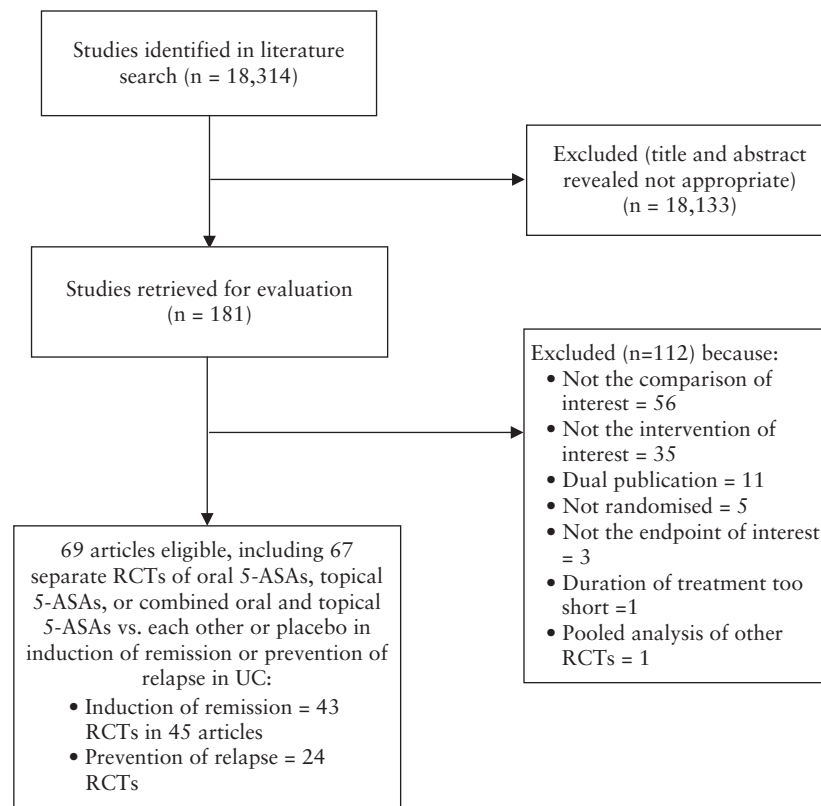


Figure 1. Flow diagram of assessment of studies identified in the network meta-analysis.

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, available as Supplementary data at ECCO-JCC online](#). Patients were allocated to active therapy or placebo as described in [Supplementary Tables 3 and 4, available as Supplementary data at ECCO-JCC online](#). 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, available as Supplementary data at ECCO-JCC online](#); 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, available as Supplementary data at ECCO-JCC online](#).

3.1. 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 $\geq 50\%$ of patients with left-sided colitis and extensive colitis,^{6,39,42,52,55,57,58,62–64,67,69,70} 16 RCTs recruited $\geq 50\%$ 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 4.8 g/day, one 4.5 g/day, six 4 g/day, and four 3.6 g/day. Among 23 RCTs using standard-dose oral mesalazine, one used 3 g/day, 17 used 2.4 g/day, two used 2.4 g/day or 2.25 g/day, one used 2.25 g/day, and two used 2 g/day. Finally, among seven trials using low-dose oral mesalazine, two used 1.6 g/day, one 1.5 g/day, two 1.2 g/day, one 1 g/day, and one 800 mg/day.

3.2. 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, available as Supplementary data at ECCO-JCC online](#). 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 probabilities 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, were 99% and 87%, respectively. However, high-dose and standard-dose oral mesalazine had the most

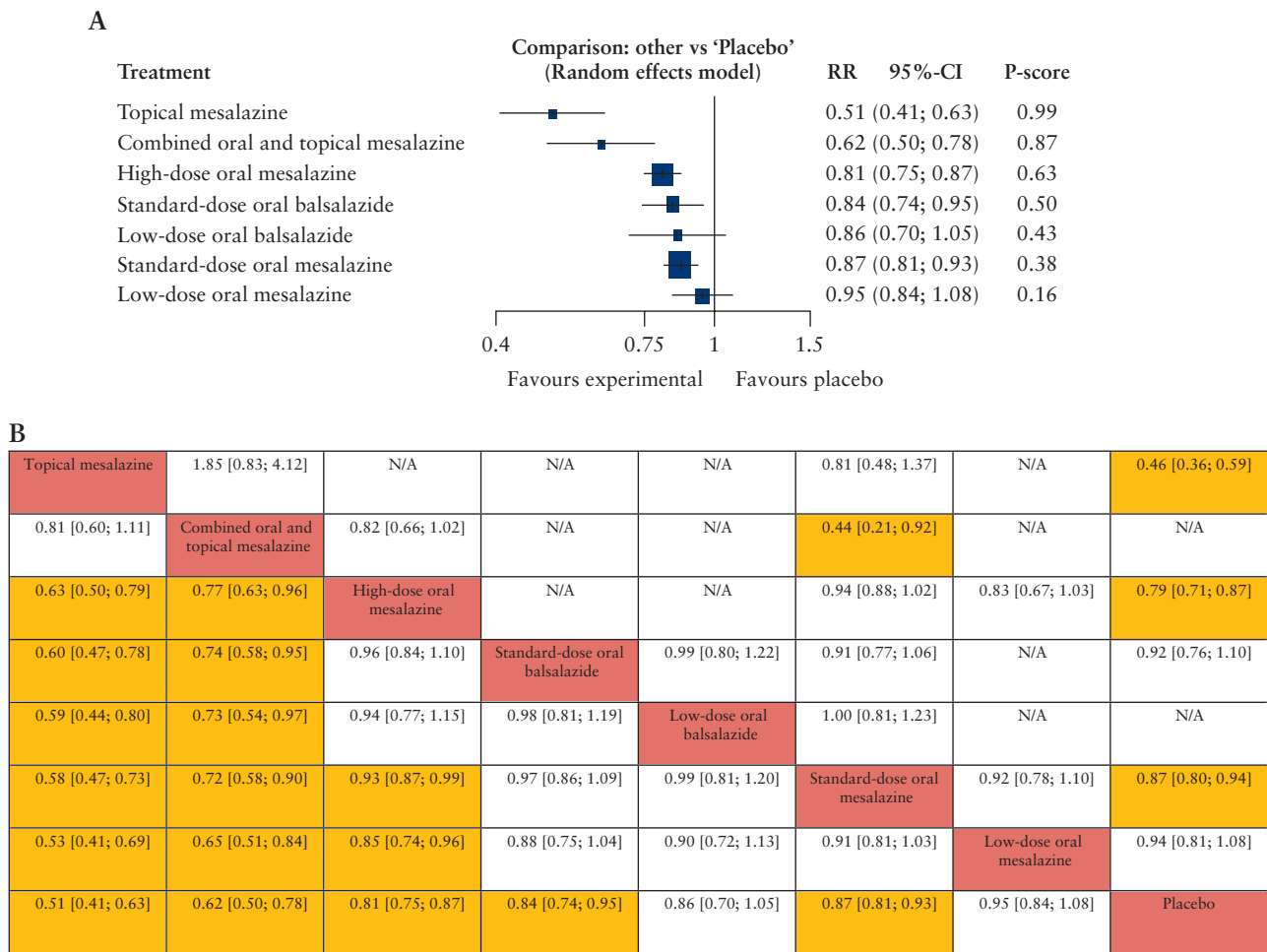


Figure 2. Network meta-analysis of likelihood of failure to achieve clinical and endoscopic remission in induction of remission trials. **A.** Forest plot for failure to achieve clinical and endoscopic remission in induction of remission trials. **B.** Summary treatment effects from the network meta-analysis for failure to achieve clinical and endoscopic remission in induction of remission trials.

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, available as Supplementary data at ECCO-JCC online], 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, available as Supplementary data at ECCO-JCC online] and was superior to high-dose and standard-dose oral mesalazine [Supplementary Figure 3B].

3.3. 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, available as Supplementary data at ECCO-JCC online. 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 =

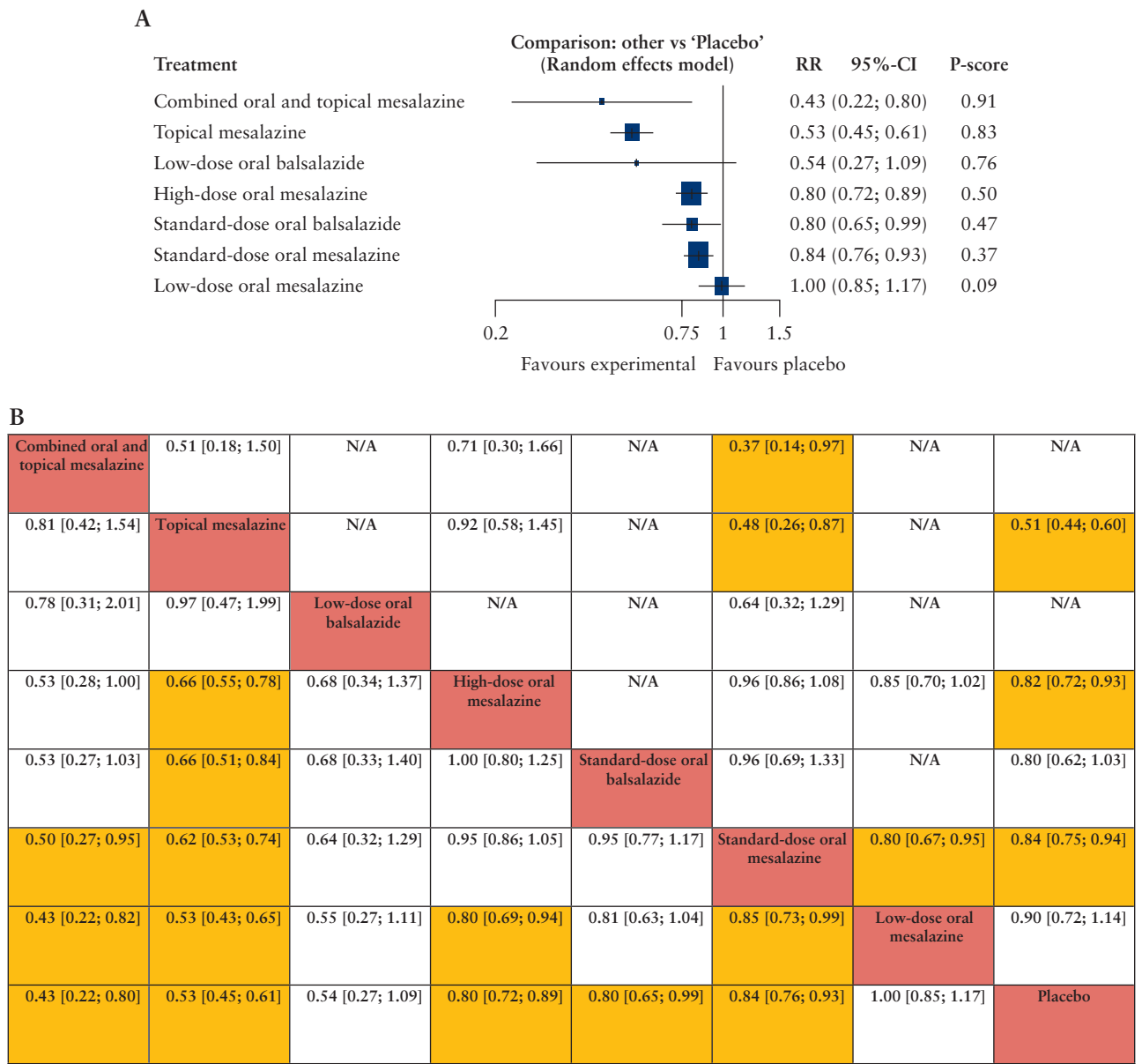


Figure 3. Network meta-analysis of likelihood of failure to achieve clinical remission in induction of remission trials. A. Forest plot for failure to achieve clinical remission in induction of remission trials. B. Summary treatment effects from the network meta-analysis for failure to achieve clinical remission in induction of remission trials.

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 that 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 which 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 which 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, available as Supplementary data at ECCO-JCC online], 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, available as Supplementary data at ECCO-JCC online]. Topical mesalazine was superior to all other therapies, except combined oral and topical mesalazine and low-dose balsalazide [Supplementary Figure 6B].

3.4. 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](#), available as [Supplementary data at ECCO-JCC online](#). 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 $\geq 50\%$ of patients with left-sided colitis or extensive colitis, and 14 trials, reported in 15 articles, recruiting $\geq 50\%$ 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](#), available as [Supplementary data at ECCO-JCC online](#)]. 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;

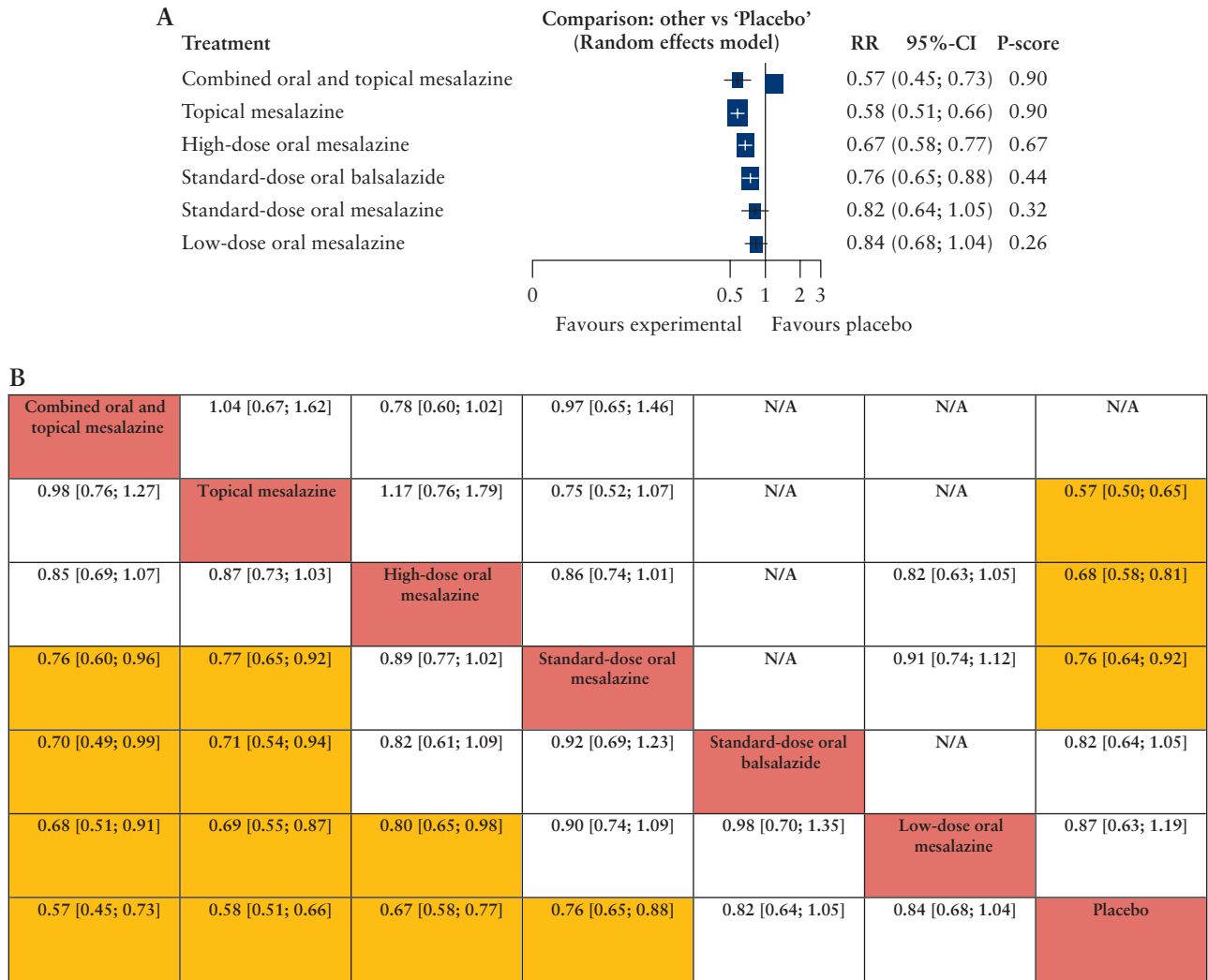


Figure 4. Network meta-analysis of likelihood of failure to achieve endoscopic remission in induction of remission trials. A. Forest plot for failure to achieve endoscopic remission in induction of remission trials. B. Summary treatment effects from the network meta-analysis for failure to achieve endoscopic remission in induction of remission trials.

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, available as Supplementary data at ECCO-JCC online]. Topical mesalazine was superior to all other therapies, except combined oral and topical mesalazine and high-dose oral mesalazine [Supplementary Figure 9B].

3.5. 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 4.8 g/day and one 4 g/day. Among six RCTs using standard-dose oral mesalazine, three used 3 g/day and three used 2.4 g/day. Finally, among 13 trials using low-dose oral mesalazine three used 1.6 g/day, one used 1.6 g/day or 800 mg/day, six 1.5 g/day, and three 1.2 g/day.

The network plot is provided in Supplementary Figure 10A, available as Supplementary data at ECCO-JCC online. 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 $\geq 50\%$ of patients with left-sided colitis and extensive colitis^{16,72,74,76-80,83,85,87,88,90-92} and eight RCTs recruiting $\geq 50\%$ 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, available as Supplementary data at ECCO-JCC online]. 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 $\geq 50\%$ 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, available as Supplementary data at ECCO-JCC online], with no difference between active therapies on indirect comparison [Supplementary Figure 12B].

4. 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 of 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 $\geq 50\%$ of patients with left-sided or extensive disease. Topical mesalazine was ranked first for most analyses in trials that recruited $\geq 50\%$ 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, high-dose oral mesalazine 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 maximise the likelihood of identifying all pertinent literature and to minimise 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 had been overestimated. The network meta-analysis allowed us to make indirect comparisons between over 4000 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 standardise 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 randomisation, 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 during which these trials were conducted, 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.

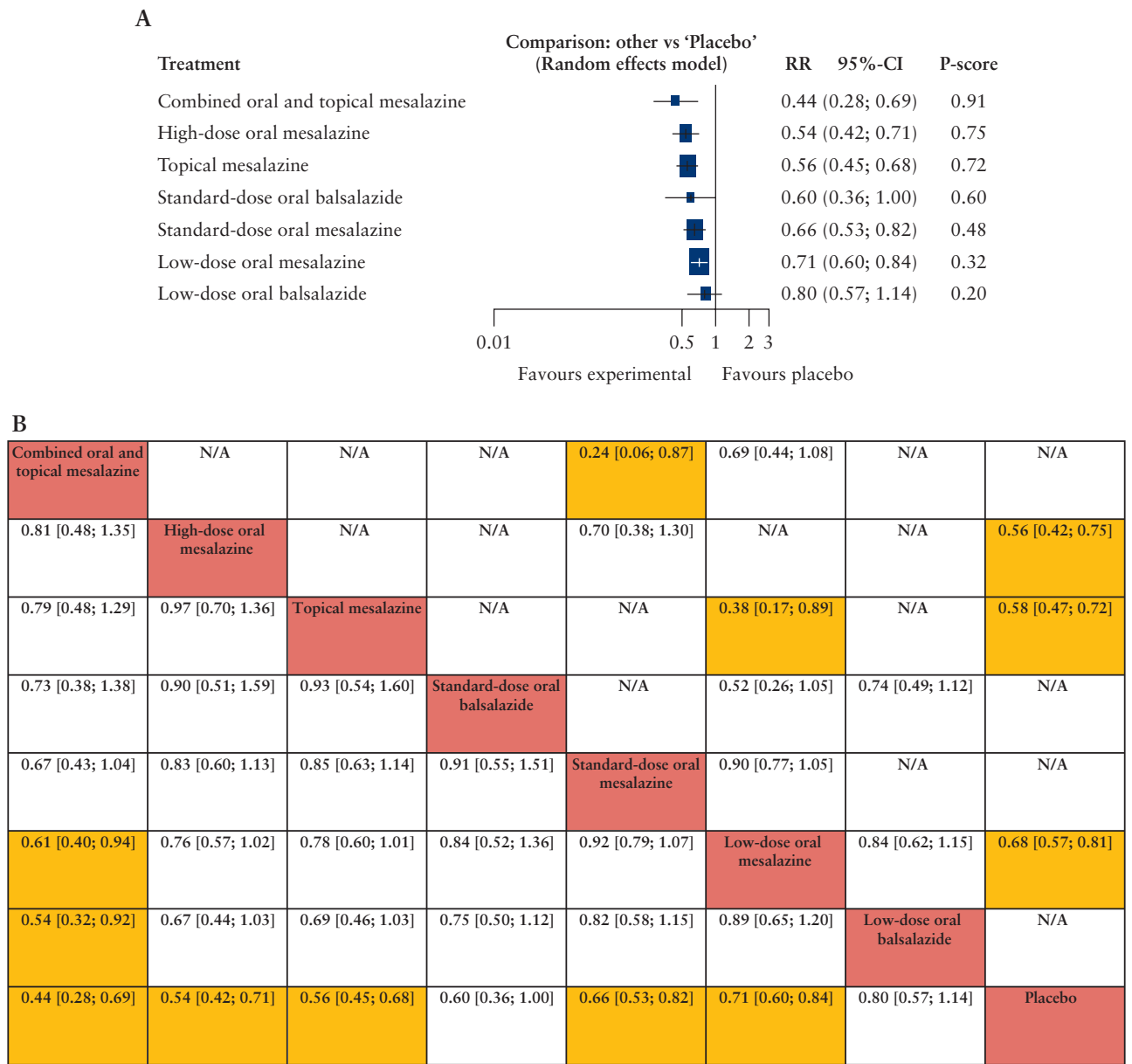


Figure 5. Network meta-analysis of likelihood of relapse of disease activity in prevention of relapse trials. A. Forest plot for relapse of disease activity in prevention of relapse trials. B. Summary treatment effects from the network meta-analysis for relapse of disease activity in prevention of relapse trials.

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, sulphasalazine, 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- (<2 g/day), standard- [2 g to 3 g/day], or high-dose [>3 g/day] 5-ASAs were different from the ones we chose, 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 [≥3.3 g/day] and standard-dose [1.7 g to 3.2 g/day] oral mesalazine for clinical and endoscopic remission combined for 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 1 g/day of topical therapy.⁹⁵ Although combined oral and topical mesalazine ranked first or second for failure to achieve induction of remission

Box 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^a with each other,^b 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^c

5-ASA, 5-aminosalicylic acid.

^aMesalazine or balsalazide.^bFor 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: ≤1.6 g/day low-dose; 1.7 g to 3.2 g/day standard-dose; ≥3.3 g/day high-dose. For oral balsalazide, which has a lower total dose of 5-ASA [1 g balsalazide delivers 0.35 g 5-ASA]¹⁶ this was as follows: ≤4.5 g/day low-dose; ≥4.6 g/day standard-dose.^cFor trials reporting failure of induction of remission we extracted data for any of the following: clinical and endoscopic remission combined [eg, 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.

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 [2 g to 3 g/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 2 g to 2.4 g/day and higher doses of 4.8 g/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 4 g/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 4 g/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 2 g/day for oral mesalazine and 3 g/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 2.4 g/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 previous 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 maximise 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 to oral 5-ASAs¹⁰⁰ 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 procto sigmoiditis.^{11,12,95} However, higher doses of oral mesalazine [≥ 3.3 g/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 ≥ 4 g/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 best 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.

Funding

None.

Conflict of Interest

None.

Author Contributions

BB, JPS, MNQ, CJB, EVS, and ACF conceived of and drafted the study. BB, JPS, MNQ, and ACF collected, analysed, and interpreted all data. BB, JPS, MNQ, and ACF drafted the manuscript. BB, JPS, MNQ, CJB, EVS, and ACF commented on drafts of the paper. All authors have approved the final draft of the manuscript.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

References

- Magro F, Gionchetti P, Eliakim R, et al.; European Crohn's and Colitis Organisation [ECCO]. 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 Crohns Colitis* 2017;11: 649–70.
- Lamb CA, Kennedy NA, Raine T, et al.; IBD guidelines eDelphi consensus group. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68:s1–s106.
- Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015;12:720–7.
- Svartz N. Ett nytt sulfonamidpreparat. Forelopande meddelande [A new sulfonamide preparation. Preliminary message]. *Nord Med* 1941;9:544.
- Das KM, Eastwood MA, McManus JP, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 1973;289:491–5.
- Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625–9.
- Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol* 2018;16:343–56.e3.
- Ford AC, Khan KJ, Achkar JP, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2012;107:167–76; author reply 177.
- Ford AC, Khan KJ, Sandborn WJ, Hanauer SB, Moayyedi P. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent ulcerative colitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:513–9.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010;20.1:CD004115.
- 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 Crohns Colitis* 2017;11:769–84.
- Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology* 2019;156:748–64.
- 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;3:742–53.
- Laasila K, Leirisalo-Repo M. Side effects of sulphasalazine in patients with rheumatic diseases or inflammatory bowel disease. *Scand J Rheumatol* 1994;23:338–40.
- Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. *Eur Respir J* 2002;19:756–64.
- 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;49:783–9.
- Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. 2011. <https://handbook-5-1.cochrane.org/> [accessed June 29, 2019].
- 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;162:777–84.
- Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17:279–301.
- 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.
- Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
- Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- 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.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;15:58.
- Morton SC, Murad MH, O'Connor E, et al. Quantitative synthesis—an update. In: *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality; 2018.

27. Powell-Tuck J, MacRae KD, Healy MJ, Lennard-Jones JE, Parkins RA. 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;92:1894–8.
29. Sandborn WJ, Hanauer S, Lichtenstein GR, Safdi M, Edeline M, Scott Harris M. 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;34:747–56.
30. Williams CN, Haber G, Aquino JA. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using 99mTc-labeled 5-ASA suppositories. *Dig Dis Sci* 1987;32:71–55.
31. Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed release 5 aminosalicylic acid [mesalazine] and sulphasalazine in the treatment of mild-to-moderate ulcerative colitis relapse. *Gut* 1988;29:669–74.
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, Ranzi T, Brunetti G, Barbara L. Mesalazine [5-aminosalicylic acid] suppositories in the treatment of ulcerative proctitis or distal proctosigmoiditis. A randomized controlled trial. *Scand J Gastroenterol* 1990;25:663–8.
34. Miglioli M, Bianchi Porro G, Brunetti G, Sturniolo GC. Delayed-release mesalazine in the treatment of mild ulcerative colitis: a dose ranging study. *Eur J Gastroenterol Hepatol* 1990;2:229–34.
35. Campieri M, Gionchetti P, Belluzzi A, *et al.* Sucralfate, 5-aminosalicylic acid and placebo enemas in the treatment of distal ulcerative colitis. *Eur J Gastroenterol Hepatol* 1991;3:41–4.
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;32:929–31.
37. Miner P, Nostrant T, Wruble L, *et al.* Multicenter trial of Pentasa for active ulcerative colitis. *Gastroenterology* 1991;100:A231.
38. Sninsky CA, Cort DH, Shanahan F, *et al.* Oral mesalazine [Asacol] for mildly to moderately active ulcerative colitis. A multicenter study. *Ann Intern Med* 1991;115:350–5.
39. Hanauer S, Schwartz J, Robinson M, *et al.* Mesalazine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. *Am J Gastroenterol* 1993;88:1188–97.
40. Safdi M, DeMicco M, Sninsky C, *et al.* A double-blind comparison of oral versus rectal mesalazine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;92:1867–71.
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;41:93–7.
42. Green JR, Lobo AJ, Holdsworth CD, *et al.* Balsalazide is more effective and better tolerated than mesalazine in the treatment of acute ulcerative colitis. The Abacus Investigator Group. *Gastroenterology* 1998;114:15–22.
43. Hanauer SB. Dose-ranging study of mesalazine [PENTASA] enemas in the treatment of acute ulcerative proctosigmoiditis: results of a multicentered placebo-controlled trial. The U.S. PENTASA Enema Study Group. *Inflamm Bowel Dis* 1998;4:79–83.
44. Pokrotnieks J, Marlicz K, Paradowski L, *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;14:1191–8.
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;15:251–6.
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 mesalazine [2.4 g] in the treatment of active, mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002;97:1398–407.
47. Malchow H, Gertz B; CLAFOAM Study group. A new mesalazine foam enema [Claversal Foam] compared with a standard liquid enema in patients with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:415–23.
48. Pruitt R, Hanson J, Safdi M, *et al.* Balsalazide is superior to mesalazine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 2002;97:3078–86.
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 mesalazine. *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;10.11:126–31.
51. Hanauer SB, Sandborn WJ, Kornbluth A, *et al.* Delayed-release oral mesalazine at 4.8 g/day [800 mg tablet] for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;100:2478–85.
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;54:960–5.
53. Probert CS, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. 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 Crohns Colitis* 2014;8:200–7.
54. Prantera C, Viscido A, Biancone L, Francavilla A, Giglio L, Campieri M. A new oral delivery system for 5-ASA: preliminary clinical findings for MMx. *Inflamm Bowel Dis* 2005;11:421–7.
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;24:1087–97.
56. Hanauer SB, Sandborn WJ, Dallaire C, *et al.* Delayed-release oral mesalazine 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;21:827–34.
57. Kamm MA, Sandborn WJ, Gassull M, *et al.* Once-daily, high-concentration MMx mesalazine in active ulcerative colitis. *Gastroenterology* 2007;132:66–75; quiz 432–3.
58. Lichtenstein GR, Kamm MA, Boddu P, *et al.* Effect of once- or twice-daily MMx mesalazine [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 mesalazine 4.8 g/day [800-mg tablet] is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009;137:1934–43.e1–3.
60. Scherl EJ, Pruitt R, Gordon GL, *et al.* Safety and efficacy of a new 3.3 g 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;104:1452–9.
61. Andus T, Kocjan A, Müser M, *et al.*; International Salofalk Suppository OD Study Group. Clinical trial: a novel high-dose 1 g mesalazine suppository [Salofalk] once daily is as efficacious as a 500-mg suppository thrice daily in active ulcerative proctitis. *Inflamm Bowel Dis* 2010;16:1947–56.
62. Ito H, Iida M, Matsumoto T, *et al.* Direct comparison of two different mesalazine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflamm Bowel Dis* 2010;16:1575–82.
63. Hiwatashi N, Suzuki Y, Mitsuyama K, Munakata A, Hibi T. 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;143:1218–26.e2.

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;145:149–57.
66. Watanabe M, Nishino H, Sameshima Y, Ota A, Nakamura S, Hibi T. 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;38:264–73.
67. Pontes C, Vives R, Torres F, Panés J. Safety and activity of darsalazine sodium in patients with mild-to-moderate active colitis: double-blind randomized proof of concept study. *Inflamm Bowel Dis* 2014;20:2004–12.
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, Hagino A, Hibi T. 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;16:255–66.
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 multicenter controlled study. *J Dig Dis* 2018;19(Suppl 1):35.
71. Sutherland LR, Martin F. 5-Aminosalicylic acid enemas in the maintenance of remission in distal ulcerative colitis and proctitis. *Can J Gastroenterol* 1987;1:1:3–6.
72. Biddle WL, Greenberger NJ, Swan JT, McPhee MS, Miner PB Jr. 5-Aminosalicylic acid enemas: effective agent in maintaining remission in left-sided ulcerative colitis. *Gastroenterology* 1988;94:1075–9.
73. D'Arienzo A, Panarese A, D'Armiento FP, *et al.* 5-Aminosalicylic acid suppositories in the maintenance of remission in idiopathic proctitis or proctosigmoiditis: a double-blind placebo-controlled clinical trial. *Am J Gastroenterol* 1990;85:9:1079–82.
74. Green JR, Swan CH, Rowlinson A, *et al.* Short report: comparison of two doses of balsalazide in maintaining ulcerative colitis in remission over 12 months. *Aliment Pharmacol Ther* 1992;6:647–52.
75. Mantzaris GJ, Hatzis A, Petraki K, Spiliadi C, Triantaphyllou G. 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 R, Nester T, *et al.* The effect of varying dose intervals of mesalamine enemas for the prevention of relapse in distal ulcerative colitis. *Gastroenterology* 1994;106:A736.
77. Fockens P, Mulder CJ, Tytgat GN, *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. Dutch Pentasa Study Group. *Eur J Gastroenterol Hepatol* 1995;7:1025–30.
78. Miner P, Hanauer S, Robinson M, Schwartz J, Arora S. Safety and efficacy of controlled-release mesalamine for maintenance of remission in ulcerative colitis. Pentasa UC Maintenance Study Group. *Dig Dis Sci* 1995;40:296–304.
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;124:204–11.
80. D'Albasio G, Pacini F, Camarri E, *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;92:7:1143–7.
81. Hawkey CJ, Dube LM, Rountree LV, Linnen PJ, Lancaster JF. A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. The European Zileuton Study Group For Ulcerative Colitis. *Gastroenterology* 1997;112:718–24.
82. d'Albasio G, Paoluzi P, Campieri M, *et al.* Maintenance treatment of ulcerative proctitis with mesalazine suppositories: a double-blind placebo-controlled trial. The Italian IBD Study Group. *Am J Gastroenterol* 1998;93:799–803.
83. Green JR, 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. ABACUS Investigator group. *Aliment Pharmacol Ther* 1998;12:1207–16.
84. Marteau P, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. *Gut* 1998;42:195–9.
85. Ardizzone S, Petrillo M, Imbesi V, Cerutti R, Bollani S, Bianchi Porro G. Is maintenance therapy always necessary for patients with ulcerative colitis in remission? *Aliment Pharmacol Ther* 1999;13:373–9.
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;95:1749–54.
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;21:1111–9.
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;13:1115–20.
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;32:990–9.
90. Kruis W, Jonaitis L, Pokrotnieks J, *et al.*; International Salofalk OD Study Group. 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;33:313–22.
91. D'Haens G, Sandborn WJ, Barrett K, Hodgson I, Streck P. Once-daily MMX[®] mesalamine for endoscopic maintenance of remission of ulcerative colitis. *Am J Gastroenterol* 2012;107:1064–77.
92. Pica R, Cassieri C, Cocco A, *et al.* A randomized trial comparing 4.8 vs. 2.4 g/day of oral mesalazine for maintenance of remission in ulcerative colitis. *Dig Liver Dis* 2015;47:933–7.
93. Gordon GL, Zakko S, Murthy U, *et al.* Once-daily mesalamine formulation for maintenance of remission in ulcerative colitis: a randomized, placebo-controlled clinical trial. *J Clin Gastroenterol* 2016;50: 318–25.
94. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;323:42–6.
95. Singh S, Feuerstein JD, Binion DG, Tremaine WJ. 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;4:CD000543.
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:e0187737.
98. Punchard NA, Greenfield SM, Thompson RP. Mechanism of action of 5-aminosalicylic acid. *Mediators Inflamm* 1992;1:151–65.
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;13:1413–7.
100. D'Incà R, Bertomoro P, Mazzocco K, Vettorato MG, Rumati R, Sturniolo GC. Risk factors for non-adherence to medication in inflammatory bowel disease patients. *Aliment Pharmacol Ther* 2008;27:166–72.
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: 381–8.
102. Ham M, Moss AC. Mesalamine in the treatment and maintenance of remission of ulcerative colitis. *Expert Rev Clin Pharmacol* 2012;5:113–23.