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Efficacy and safety of medical therapies in microscopic colitis: a systematic review and network meta-analysis

Aditi Kumar*, George Hiner*, Matthew J. Brookes and Jonathan P. Segal

Abstract

Background: The mainstay of treatment for microscopic colitis (MC) is budesonide. However, the optimal formulation and dosage of budesonide to induce and maintain remission has not yet been clearly demonstrated.

Objectives: To compare the data for efficacy and safety of treatments to induce and maintain remission for MC.

Design: We conducted a meta-analysis of randomised controlled trials (RCTs) comparing treatment with each other or placebo for induction and maintenance of clinical and histological remission in MC.

Data sources and methods: We searched MEDLINE (1946 to May 2021), EMBASE and EMBASE Classis (1947 to May 2021), the Cochrane central register of controlled trials (Issue 2, May 2021) and conference proceedings between 2006 and 2020. Results were reported as pooled relative risks (RRs) with 95% confidence intervals (CIs) to summarise the effect of each comparison tested, with treatments ranked according to p score.

Results: We identified 15 RCTs in total for the treatment of MC. Entocort 9 mg ranked first for clinical (RR: 4.89, CI: 2.43–9.83; p score: 0.86) and histological (RR: 13.39, CI: 1.92–93.44; p score 0.94) induction of remission, whilst VSL#3 ranked second for clinical induction (RR: 5.30, CI: 0.68–41.39; p score 0.81). Budenofalk 6 mg/3 mg alternate day dosing ranked first for clinical maintenance of remission (RR: 3.68, CI: 0.08–159.92, p-score 0.65). Entocort and Budenofalk were associated with the greatest adverse events for induction and maintenance of clinical remission, respectively, although the overall withdrawal numbers for treatment *versus* placebo groups were 10.9% (22/201) and 10.5% (20/190), respectively.

Conclusion: Entocort 9 mg/day ranked first among the treatment options in inducing remission and Budenofalk 6 mg/3 mg alternate day dosing for maintaining remission in the treatment of MC. Moving forward, mechanistic studies exploring the differences between Entocort and Budenofalk would be valuable whilst future RCT studies are needed in non-corticosteroidal maintenance, particularly looking into immunomodulators, biologics and probiotics.

Keywords: Budenofalk, budesonide, corticosteroids, Entocort, microscopic colitis

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Correspondence to:
Aditi Kumar
Department of Gastroenterology, The Royal Wolverhampton NHS Trust, Wolverhampton Road, Wolverhampton, West Midlands wv10 0qp, UK
aditikumar@nhs.net

George Hiner
Department of Gastroenterology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

Matthew J. Brookes
Department of Gastroenterology, The Royal Wolverhampton NHS Trust, Wolverhampton, UK

School of Medicine and Clinical Practice, Faculty of Sciences and Engineering, University of Wolverhampton, Wolverhampton, UK

Jonathan P. Segal
Department of Gastroenterology, Northern Hospital, Epping, VIC, Australia

*AK and GH are joint first co-authors

Introduction

Microscopic colitis (MC) was first reported in 1980 and is now a well-recognised form of inflammatory bowel disease.[1] Symptoms include chronic watery, non-bloody diarrhoea that may continue from months to years. Faecal urgency, incontinence and abdominal pain can also be seen.[2,3] Previously, the prevalence of MC was likely to have been under estimated as a proportion of patients were diagnosed with irritable bowel syndrome without further investigation. Prevalence now is felt to be between 50 and 200/100,000,[4] with women affected approximately 2:1 and a mean age of presentation around 60. It carries a benign course

without increase in mortality, nor increased risk of colorectal cancer. However, it can be debilitating and have a profound effect on quality of life.[5]

The mainstay of treatment has been budesonide, a locally active corticosteroid with extensive first-pass hepatic metabolism avoiding significant systemic absorption. However, the optimal formulation and dosage of budesonide to induce and maintain remission has not been clearly demonstrated. Whilst the European guidelines recommend 9 mg budesonide/day for induction and 6 mg budesonide/day for maintenance,[2] the American guidelines state budesonide should be used for induction and maintenance but do not provide specific guidelines on dose.[3] Neither guideline differentiates between the varying formulations offered on the market, such as Budenofalk, Entocort and Cortiment. Although there have been randomised controlled trials (RCTs) that investigate this, the numbers have been too small to offer a definitive answer. Similarly, there is inadequate data for determining the benefit of other medications such as aminosalicylates, probiotics and prednisolone.

In this meta-analysis, we aim to compare the data for efficacy and safety of treatments, trialled in RCTs, to induce and maintain clinical remission for MC.

Methods

Search strategy and study selection

A search of the medical literature was conducted using MEDLINE (1946 to May 2021), EMBASE and EMBASE classic (1947 to May 2021), the Cochrane central register of controlled trials (Issue 2, May 2021) and the Cochrane 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 medical therapies *versus* placebo or another therapy for MC were included. We included only an adult population where at least 90% of the subjects were over 16 years old. For 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. To be considered as induction remission, duration of therapy was 10 weeks or less and greater than 10 weeks for maintenance remission. The study protocol was published on the PROSPERO international prospective register of systematic reviews in May 2021 (Reference number: 256376). Ethical approval for this study was not required.

Studies were identified with the terms 'microscopic colitis', 'lymphocytic colitis' or 'collagenous 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 (see Supplemental Appendix 1). There were no language restrictions and we translated manuscripts where appropriate. The abstracts from the search were screened against eligibility criteria and those that were deemed to potentially fit was examined in greater detail using the whole manuscript. Eligibility assessment was performed by two independent authors (AK and GH) using pre-defined eligibility forms. We resolved any disagreements by consensus and discussion with a third author (JPS).

Outcome assessment

The primary outcome was the efficacy of medical therapies at inducing and maintaining remission in symptomatic active MC. Secondary outcomes included adverse events (AEs) occurring due to therapy, including total number of patients who had AEs and AEs leading to study withdrawal.

Treatment modalities that were compared include corticosteroids (prednisolone and budesonide), aminosalicylates (mesalazine), probiotics, bile acid sequestrants (cholestyramine) and herbal medication [Boswellia serrata extract (BSE)]. When possible, where studies that sub-classified budesonide, further analyses were done to categorise its different formulations including Budenofalk, Entocort and Cortiment. Probiotics included were either an enhanced probiotic mixture containing eight bacterial strains (in this manuscript known as probiotic) or a probiotic mixture containing *Bifidobacterium animalis* subsp *lactis BB-12* (known as AB-CAP-10).

Definitions

Clinical induction and/or maintenance of remission was defined as either stool frequency equal to

or less than 3 stools/day on average within the preceding 7 days prior to assessment; stool weight <200 g/day or a decrease in stool frequency or stool weight by of at least 50%. Induction was defined as treatment given for less than 10 weeks whilst maintenance of remission was defined as treatment given for greater than 10 weeks.

Histological remission was defined using several parameters: reduction in the mean thickness of collagen band of less than 10 µm, reduction if infiltrate in lamina propria (the number of intraepithelial lymphocytes (IELs) less than or equal to 20 IEL/100 epithelial cells), and the absence of the degeneration of the surface epithelium.

Data extraction

Data were extracted onto a Microsoft excel spreadsheet by two independent investigators (AK and GH) as dichotomous outcomes (remission or failure of remission). Discrepancies were resolved with a third author (JPS).

We extracted the following clinical data for each trial, where available: endpoints used to define remission or relapse, dosage, route, and schedule of medication used, duration of therapy, and number of individuals incurring each (or any) of the AEs of interest. Where individual trials used more than one endpoint to define 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 MC). See Supplemental Materials for full study extraction data.

Quality assessment and risk of bias

We used the revised Cochrane Risk of Bias tool for randomised trials (RoB 2 tool) to assess the quality of studies.[6,7] Two investigators (AK and GH) 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.[8]

We generated comparison-adjusted funnel plots to asses publication bias and small-study bias for all available treatment comparisons *versus* each other or placebo, where sufficient studies (⩾10) existed. If symmetry around the effect estimate line is found, then this indicates the absence of publication bias or small-study bias.[9]

For each treatment in the meta-analysis, we generated a pooled relative risk (RR) with 95% confidence intervals (CIs) to compare the effect of each comparison tested using a random effects model. We calculated the RR of failure to achieve remission where values <1 and the 95% CI did not cross 1 highlights that there is a significant benefit of one treatment over another, or over placebo. In situations where event rates were 0, a value of 0.5 was added to each arm of the study to enable RR calculations. There were direct comparisons between some of the treatments for several endpoints of interest. For AEs and withdrawals, we calculated RR with ascending p scores correlating with increase rates of events or withdrawals. Hence, those ranked highest represented the drugs with the highest AEs or withdrawals.

We then assessed global statistical heterogeneity using the I^2 measure. The I^2 measure of heterogeneity ranges from 0% to 100%. A result of 25–49% indicates low study heterogeneity, 50–74% indicates moderate heterogeneity, and 75% and above indicates high heterogeneity.[10]

Heat plots were also used to assess inconsistency in the network meta-analysis by comparing direct and indirect evidence (when available). The grey squares in these plots represent the size of the contribution of the direct estimate in columns, compared with the network estimates in rows.[11] The coloured squares represent the degree of inconsistency.

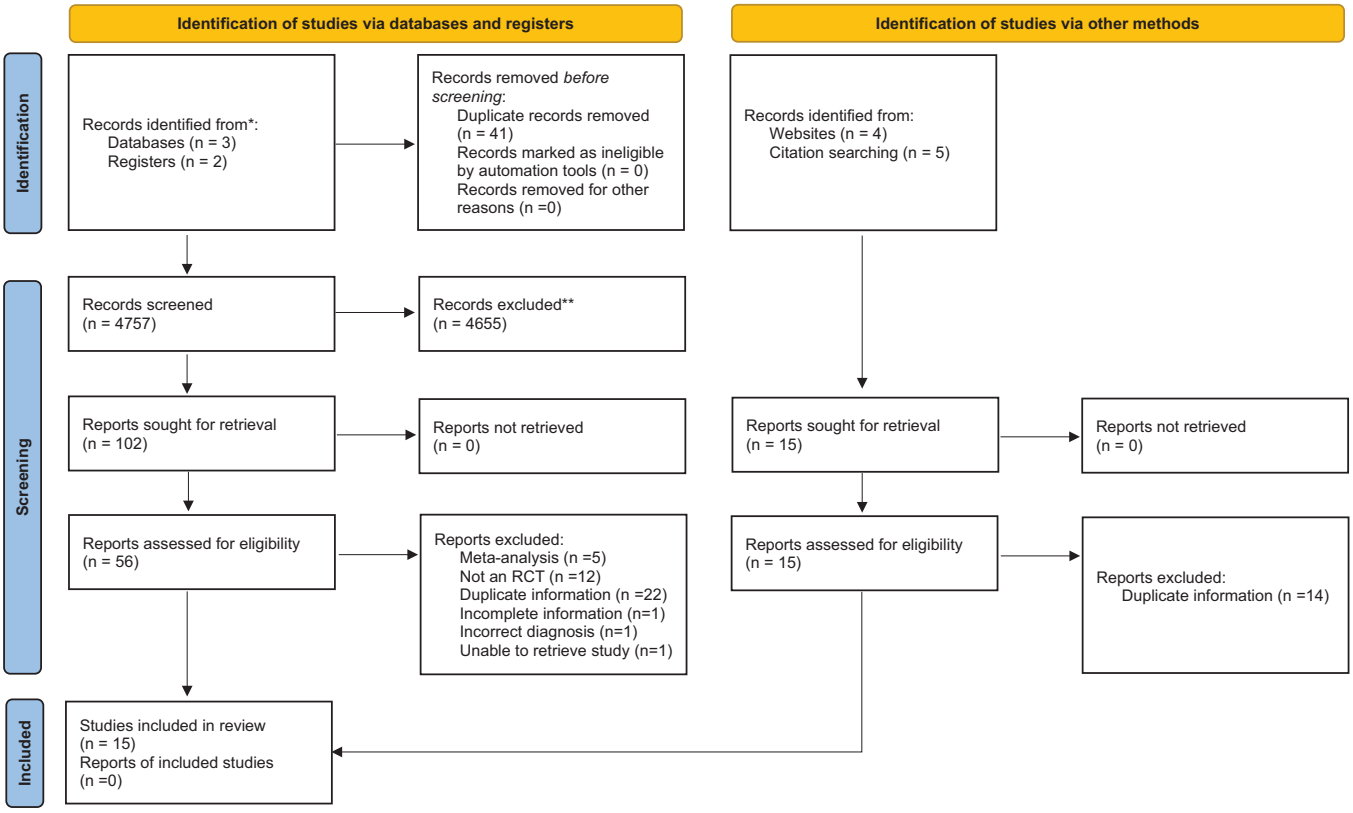

Figure 1. PRISMA diagram of the identification of studies.
Source: Page *et al.*[13]

The p score was used to rank treatments which generates a value between 0 and 1. They measure the extent of certainty that one treatment is superior to another. The higher the score, the more likely they are superior to another treatment.[12]

Role of the funding source

This study received a £10,000 grant from Tillots. All the authors had full access to all the data in the study and had cumulative final responsibility for the decision to submit for publication.

Results

The literature search found 4749 relevant screening articles. After the abstract screening, this was reduced to 94 leaving 57 for full-text screening and final 15 articles were included in the network meta-analysis accounting for a total of 643 patients. Figure 1 elaborates on the study screen search with the PRISMA flow diagram. Data extraction from each study can be accessed in the Supplemental Materials.

Clinical induction studies

In the induction remission trials, a total of 10 RCT studies were included accounting for a total of 378 patients, with 215 in the treatment group and 163 in the placebo group.[14–23] In all, 84 patients were randomised to Budenofalk, 47 to Entocort, 44 to mesalazine, 16 to BSE, 15 to a probiotic mixture containing eight bacterial strains and 9 to prednisolone. The network graph of treatment comparisons can be seen in the Supplemental Materials. Entocort 9 mg was ranked first with a RR of 4.89 (CI: 2.43–9.83, p-score 0.86), whilst VSL#3 was second with a RR of 5.30 (CI: 0.68–41.39; p score 0.81). Budenofalk (RR: 1.56, CI: 1.23–1.98; p score 0.51) ranked third and both Budenofalk and Entocort were shown to have significantly greater efficacy than placebo. Mesalazine ranked lowest with a RR of 1.06 (CI: 0.74–1.51; p score 0.21). See Figures 2(a) and 3(a) for full breakdown of medication efficacy compared to placebo. Quantifying heterogeneity/inconsistency: $\text{mtau}^2 = 0$; $\text{tau} = 0$; and $I^2 = 0\%$ [0.0–74.6%]. There was limited heterogeneity in the studies included [$I^2 = 0\%$

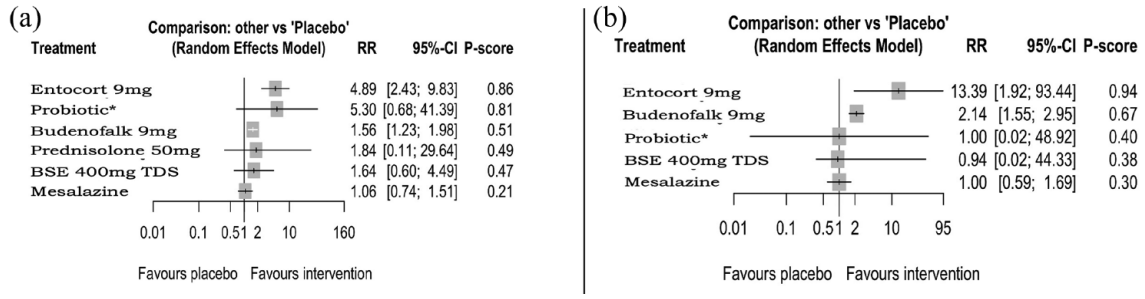

Figure 2. (a) Forest plot for induction of clinical remission trials. (b) Forest plot for induction of histological remission trials.
*Probiotic is a mixture of eight bacterial strains.
BSE, Boswellia serrata extract.

(a)

ENTOCORT 9MG	.	.	.	.	.	4.8891 (2.4321; 9.8285)
0.9225 (0.1053; 8.0844)	PROBIOTIC*	.	.	.	5.0000 (0.6605; 37.8519)	.
3.1343 (1.4998; 6.5503)	3.3978 (0.4384; 26.3368)	BUDENOFALK 9MG	.	.	1.4687 (1.0741; 2.0083)	1.5753 (1.2436; 1.9956)
2.6541 (0.1513; 46.5521)	2.8772 (0.0908; 91.1501)	0.8468 (0.0521; 13.7600)	PREDNISOLONE 50MG	.	.	1.8421 (0.1145; 29.6352)
2.9800 (0.8754; 10.1442)	3.2306 (0.3276; 31.8530)	0.9508 (0.3382; 2.6733)	1.1228 (0.0585; 21.5544)	BSE 400mg TDS	.	1.6406 (0.5997; 4.4886)
4.6123 (2.1065; 10.0987)	5.0000 (0.6605; 37.8519)	1.4715 (1.0793; 2.0063)	1.7378 (0.1056; 28.5986)	1.5477 (0.5322; 4.5009)	MESALAZINE	0.9832 (0.6597; 1.4654)
4.8891 (2.4321; 9.8285)	5.3002 (0.6787; 41.3888)	1.5599 (1.2318; 1.9753)	1.8421 (0.1145; 29.6352)	1.6406 (0.5997; 4.4886)	1.0600 (0.7427; 1.5130)	PLACEBO

(b)

ENTOCORT 9MG	.	.	.	.	13.3913 (1.9191; 93.4419)
6.2671 (0.8745; 44.9124)	BUDENOFALK 9MG	.	.	2.1114 (1.3676; 3.2597)	2.1335 (1.5444; 2.9473)
13.3779 (0.1731; 1033.7296)	2.1346 (0.0442; 103.1996)	PROBIOTIC*	.	1.0000 (0.0212; 47.1834)	.
14.2841 (0.1904; 1071.6965)	2.2792 (0.0476; 109.2305)	1.0677 (0.0045; 255.2578)	BSE 400mg TDS	.	0.9375 (0.0198; 44.3264)
13.3779 (1.7901; 99.9796)	2.1346 (1.3835; 3.2936)	1.0000 (0.0212; 47.1834)	0.9366 (0.0191; 45.8606)	MESALAZINE	0.9568 (0.5436; 1.6840)
13.3913 (1.9191; 93.4419)	2.1368 (1.5469; 2.9515)	1.0010 (0.0205; 48.9151)	0.9375 (0.0198; 44.3264)	1.0010 (0.5946; 1.6853)	PLACEBO

Figure 3. (a) Summary treatment effects from the network meta-analysis for induction of clinical remission trials. (b) Summary treatment effects from the network meta-analysis for induction of histological remission trials.
*Probiotic is a mixture of eight bacterial strains.
BSE, Boswellia serrata extract.

(CI: 0–74.6%)] but this was associated with large CIs. Egger's test was $p=0.4295$ which demonstrates that there was no evidence of publication bias (Figure 5(a)). There were not enough studies to perform a heat plot.

Induction histology

There were seven RCTs included in the analysis of the induction of histological remission network meta-analysis.[14,17–20,22,23] A total of 264 patients were included, of which 152 patients were randomised to six different treatments. In all, 66 patients had Budenofalk, 32 had mesalamine, 23 had Entocort, 16 had BSE and 15 had a probiotic mixture containing eight bacterial strains. Entocort ranked highest and was shown to have a significantly greater efficacy than placebo with a RR of 13.39 (CI: 1.92–93.44; p score 0.94; Figures 2(b) and 3(b)). This was followed

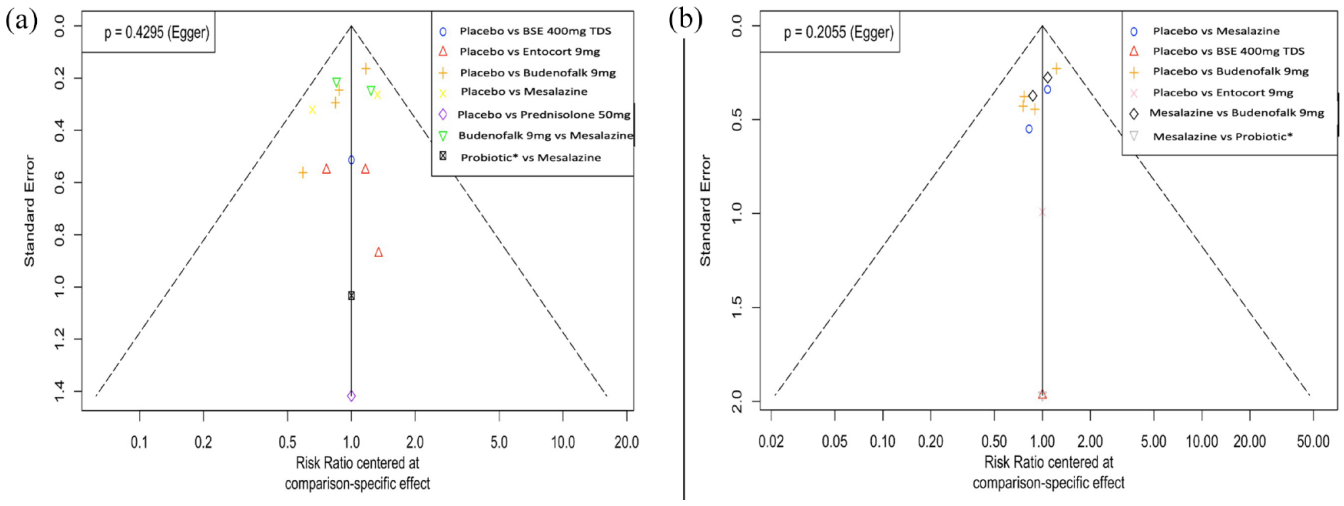

Figure 4. (a) Funnel plot for clinical induction of remission trials. (b) Funnel plot for histological induction of remission trials.
*Probiotic is a mixture of eight bacterial strains.

by Budenofalk (RR: 2.14, CI: 1.55–2.95; p score 0.67). Mesalamine was ranked lowest with a RR of 1.00 (CI: 0.59–1.69; p score 0.30). The $I^2 = 0\%$ (95% CI: 0.0–79.2%). Egger's test p value was 0.2055 indicating no evidence of publication bias (Figure 4(b)). The Netheat plot for histological remission is shown in the Supplemental Materials.

Induction AEs

From the initial 10 RCT studies that reported on clinical induction, one study did not comment on AE[15] and two studies reported total AE rather than the number of patients with AE.[16,18] Of the remaining seven studies, a total of 318 were included (see Supplemental Materials).[14,17,19–23] 69/182 (37.9%) patients on treatment and 39/136 (28.7%) patients on placebo experienced AE. Entocort 9 mg ranked the highest number of AE (10/37, 27%) with a RR of 2.64 (CI: 0.87–8.06; p score 0.86). This was followed by mesalamine (30/44, 68%, RR: 1.34, CI: 0.96–1.87; p score 0.65), BSE 400 mg three times daily (2/16, 12.5%, RR: 1.88, CI: 0.19–18.6; p score 0.64), Budenofalk 9 mg (25/70, 35.7%, RR: 0.91, CI: 0.62–1.34; p score 0.26) and a probiotic mixture containing eight bacterial strains (2/15, 13.3%, RR: 0.67, CI: 0.14–3.24; p score 0.23). The results were found to be all non-significant. The $I^2 = 0\%$ (0.0–79.2%). Egger's test was 0.4534 indicating no evidence of publication bias. There were not enough studies to produce a heat plot.

Induction withdrawals

There were 10 RCTs that reported on induction withdrawals.[4,14–20,22,23] 18/215 (8.4%) patients on treatment and 12/163 (7.4%) patients on placebo withdrew from their respective studies. BSE 400 mg TDS ranked highest for study withdrawals with 4/16 (25%) and a RR of 8.45 (CI: 0.49–144.46; p score 0.91). This was followed by the probiotic mixture containing eight bacterial strains (0/15) with a RR of 0.82 (CI: 0.01–44.76; p score 0.46), mesalazine (4/59, 6.8%) with a RR of 0.82 (CI: 0.28–2.39; p score 0.44), Entocort 9 mg (4/47, 8.5%) with a RR of 0.77 (CI: 0.23–2.61; p score 0.42), Budenofalk 9 mg (6/84, 7.1%) with a RR of 0.78 (CI: 0.31–1.97; p score 0.41), and prednisolone 50 mg (0/9) with a RR of 0.33 (CI: 0.01–13.43; p score 0.29). These results were all non-significant. The I^2 was 0% (95% CI: 0–76). Egger's test $p = 0.8789$ showing no evidence of funnel plot asymmetry. There were not enough studies for a heat plot.

Maintenance of clinical remission

There were five RCTS included in the meta-analysis for maintenance of clinical remission.[24–28] A total of 201 patients were included, of which 105 were on treatment and 96 were given placebo. Of the treatment groups, 40 had Entocort 6 mg, 44 had Budenofalk 6 mg/3 mg alternate day dosing and 21 had probiotics (*Lactobacillus acidophilus LA-5* and *Bifidobacterium animalis* subsp *lactis BB-12*, AB-CAP-10). Budenofalk 6 mg/3 mg ranked first

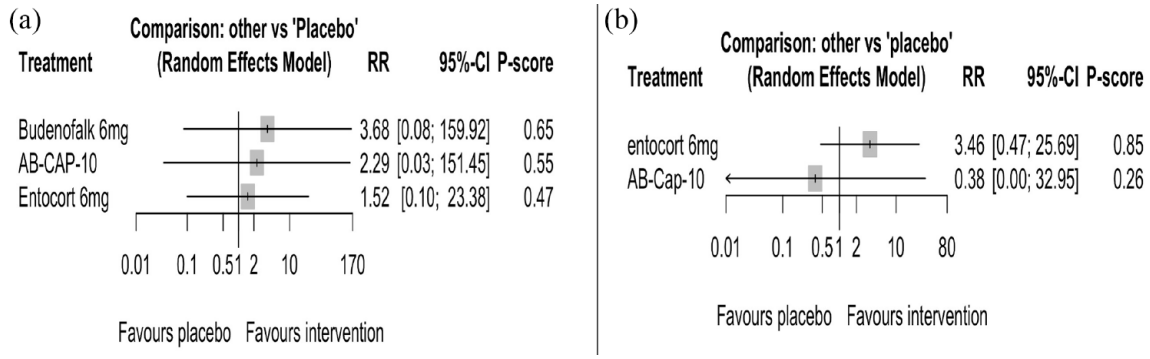

Figure 5. (a) Forest plot for clinical maintenance of remission trials. (b) Forest plot for histological maintenance of remission trials.
*AB-CAP-10: probiotic mixture of *Lactobacillus acidophilus* strain LA-5 and *Bifidobacterium animalis subsp Lactis* strain BB-12.

(RR: 3.68, CI: 0.08–159.92; p score 0.65), followed by AB-CAP-10 (RR: 2.29, CI: 0.03–151.45; p score 0.55) and Entocort 6 mg (RR: 1.52, CI: 0.10–23.38; p score 0.47) (Figures 5(a) and 6(a)). The results were all found to be non-significant. Due to the small number of studies, I^2 could not be calculated. Egger's test also could not be calculated due to the small number of studies. The netheat plot for maintenance of clinical remission can be found in the Supplemental Materials. One comparison study, mesalazine *versus* mesalazine and cholestyramine (Calabrese *et al.*[27]), could not be included in the network meta-analysis due to there being no direct or indirect correlations. In this study, patients were randomised to receive either mesalazine 800 mg TDS alone or with cholestyramine 4 g once daily for a period of 6 months. The results showed that 26/31 (83.4%) patients on mesalazine alone maintained remission, whilst 30/33 (90.9%) patients in the combined mesalazine/cholestyramine group maintained remission.

Maintenance of histological remission

There were two RCTs included in the maintenance for histological remission,[24,25,28] accounting for a total of 55 patients, of which 33 were on treatment and 22 were given placebo. There were 25 patients taking Entocort 6 mg and 8 patients taking AB-CAP-10. Entocort ranked highest with a RR of 3.46 (CI: 0.47–25.69; p score = 0.85) followed by AB-CAP-10 (RR: 0.38, CI: 0.00–32.95; p score 0.26) (Figures 5(b) and 6(b)). None of the results were significant. There were not enough studies to perform a funnel plot or heatmap.

Maintenance AEs

There were four RCTs that reported on AEs during maintenance treatment.[24–28] There was a total of 44/115 (38.2%) patients who experienced AE on treatment and 42/121 (34.7%) patients on placebo. Patients on Budenofalk 6 mg/3 mg alternate day dosing ranked the highest for experiencing AE (31/44, 70.5%) with a RR of 1.41 (CI: 1.0–1.98; p score 0.96). 13/40 (32.5%) of patients on Entocort 6 mg/day experienced AE with a RR of 0.81 (CI: 0.45–1.47; p score = 0.15); however, this was not significantly worse than the AE experienced with placebo. The I^2 was unable to be calculated. There were not enough studies to perform a funnel plot or heatmap.

Maintenance withdrawals

There were five RCTs that reported on patients withdrawing from their respective studies whilst on maintenance treatment.[24–28] Of the patients on maintenance treatment, a total of 9/136 (6.6%) patients withdrew their studies whilst 9/129 (7%) withdrew with placebo. Although Entocort 6 mg ranked highest for patient withdrawals [4/40 (10%), RR: 1.94, CI: 0.35–10.57; p score = 0.75], which was followed by AB-CAP-10 [1/21 (4.8%), RR: 1.19, CI: 0.05–26.34; p score = 0.53) and Budenofalk 6 mg/3 mg alternate dosing [4/44 (9.1%), RR: 0.62, CI: 0.20–1.99; p score = 0.23), none of the results were significant when compared with placebo. There were not enough studies to calculate the I^2 or perform a funnel plot or heatmap.

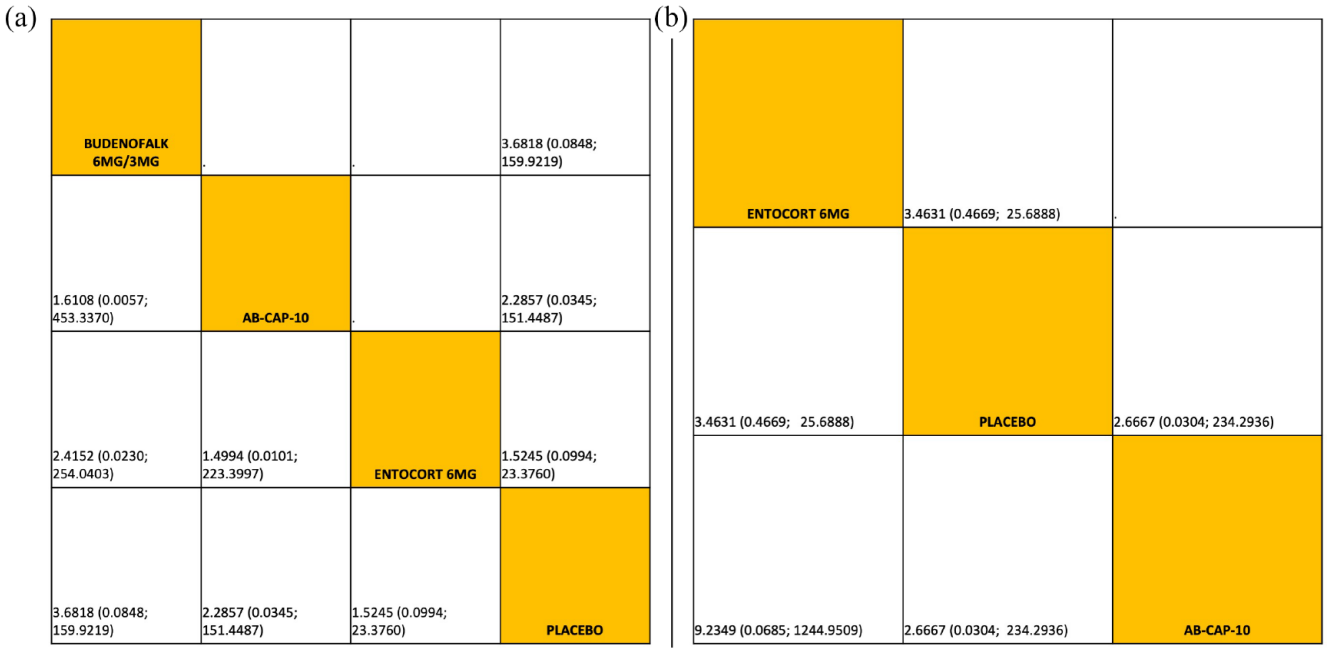

Figure 6. (a) Summary treatment effects from the network meta-analysis for maintenance of clinical remission trials. (b) Summary treatment effects from the network meta-analysis for maintenance of histological remission trials.
*AB-CAP-10: probiotic mixture of *Lactobacillus acidophilus* strain LA-5 and *Bifidobacterium animalis subsp Lactis* strain BB-12.

Discussion

To our knowledge, this is the first network meta-analysis that ranks treatment modalities for MC. Our results demonstrated that Entocort 9 mg/day ranked first in inducing clinical and histological remission whilst Budenofalk 6 mg/3 mg alternate day dosing was superior in maintaining clinical remission. Whilst Budenofalk was superior in maintaining clinical remission, like all the other treatments, this was non-significant. Our study also demonstrated that there was no beneficial effect with aminosalicylates. These results provide greater clarity than the current American guidelines which do not specify dosage of budesonide for induction and maintenance treatment,[3] and the European guidelines which recommend budesonide 9 mg/day for induction and 3–6 mg/day for maintenance, without distinguishing between the different brands available on the market.[2] A more recent population-based study published in 2022 demonstrated complete response in 80% of patients treated with budesonide with 63% having recurrence following discontinuation.[29] 58% of the patients who had recurrence required long-term budesonide maintenance treatment with 98% of patients achieving long-term complete response. Whilst this study demonstrated long-term use of budesonide to be safe and effective, the study did not provide details on budesonide dosing. Furthermore, one-quarter of patients were treated concomitantly with budesonide and another medication for induction, including loperamide, bismuth salicylate and bile acid sequestrants, thereby limiting any conclusive statement on the benefit of budesonide alone.

Budesonide is a second-generation corticosteroid with a strong anti-inflammatory action and low systemic bioavailability due to its (90%) first-pass hepatic metabolism.[30] Thus, compared to systemic corticosteroids, budesonide has a much lower incidence of systemic AE with the most common side effects reported being Cushingoid features and hypokalaemia.[31] Whilst Entocort was effective in inducing remission of MC, we found this medication to be associated with the highest number of AE. In the maintenance studies, Budenofalk was associated with the most AE whilst Entocort was associated with the greatest withdrawals. However, the results were all non-significant when compared with placebo and the overall withdrawal numbers for treatment *versus* placebo groups were 10.9% (22/201) and 10.5% (20/190), respectively. Thus, these results should be interpreted with caution.

Budesonide is available in different oral formulations: controlled ileocolonic-release formulation characterised by pH and time-dependent release (Entocort), pH dependent-release formulation (Budenofalk) and multimatrix (MMX) formulation (Cortiment).[32] The first two formulations release the drug to the terminal ileum and ascending colon whilst the MMX formulation has a controlled rate of release throughout the colon.[33] Our study highlighted that Entocort was more effective in inducing clinical remission whilst Budenofalk was more effective in maintaining clinical remission. The reasoning as to why there was a difference between these two formulations that ultimately release the drug in the same location is unknown. Furthermore, it is difficult to make any conclusive statements considering the studies were underpowered. Nonetheless, the results warrant larger studies to compare these two drugs and to determine whether there is a true treatment effect difference. If a true effect is seen, then further mechanistic studies should be carried out to explore these findings. There were no reported studies on the MMX formulation and this may be an interesting area to highlight for further research in the future.

Whilst our study explored treatment preference for histological remission, the number of RCTs that explored this outcome was very small and the CIs were very wide. Therefore, the results should be interpreted with caution until greater data are published in the literature. We also recommend future studies that explore whether histological remission should be an outcome to drive therapy, as this is currently uncertain[34–36] and subsequently not recommended by the European Guidelines.[2]

The probiotic containing eight bacterial strains including *Bifidobacterium, Lactobacillus* and *Streptococcus* and the probiotic AB-CAP-10 ranked second for inducing and maintaining clinical remission, respectively. However, study numbers were small and results were non-significant; therefore, these results must be interpreted with a great deal of caution. In the RCT by Rohatgi *et al.*,[22] they demonstrated significantly reduced stool frequency, stool weight and diarrhoeal rate with the use of the probiotic containing eight bacterial strains but no significant improvement in stool consistency and abdominal pain. In the AB-CAP-10 study, 6/21 patients given probiotics had >50% reduction in bowel frequency per week compared to 1/8 in the placebo group ($p = 0.635$) with no differences between treatments for changes in bowel frequency, stool consistency, stool weight, abdominal pain and bloating, or histopathology of biopsies from the sigmoid colon.[28] Due to the very limited studies, probiotics have yet to demonstrate treatment efficacy and as such, they are not recommended for treating MC.[2,37]

There are limitations to this study. Our conclusions are limited by the quality of the included trials with only three ranked as low risk of bias across all domains (see Supplemental Materials). The majority of studies did not adequately describe their randomisation process, particularly in describing their randomisation and treatment allocation process. It is well known that studies that insufficiently report their methodology can be associated with an over exaggeration of their treatment effects.[38] Furthermore, the studies included were limited by small numbers in individual studies with a wide range of 95% CI. Thus, the results of this meta-analysis should be interpreted with caution. Network meta-analysis methodology requires RCTs that have common comparison arms to rank treatments. Therefore, our study does not include further evidence from case studies and case series, which may have provided some important aspects on optimum treatments. One further criticism is that the studies included are mainly Western population RCTS and therefore the results may not be generalisable to the global population. The major strength of this study, however, is that it is the first meta-analysis to pool all the RCTs together with the different formulations of budesonide and rank treatments according to common comparisons.

The management of MC remains an area of ongoing research. Kafil *et al.*[37] and Chande *et al.*[39] conducted separate meta-analyses studies, demonstrating efficacy with budesonide in the induction and remission of treatment for both lymphocytic and collagenous colitis, respectively. Neither study, however, could provide conclusive evidence on other treatment modalities due to low-quality evidence. Sebastian *et al.*[40] also conducted a meta-analysis, demonstrating efficacy with budesonide in MC. Their study did not discriminate between the sub-types of MC, and did not differentiate between the different brands of Entocort and Budenofalk. Although the study numbers were small, our systematic review and network meta-analysis demonstrated that

Entocort 9 mg/day ranked first in inducing remission and Budenofalk 6 mg/3 mg alternate day dosing for maintaining remission in the treatment of MC. Prednisolone and 5-aminosalicylic acids were not shown to be effective. However, before we can confidently state that Entocort and Budenofalk are the preferred medications for MC, larger studies with smaller 95% CI are needed. In addition, moving forward, further studies are needed to explore the mechanism behind the different formulations of budesonide and future RCT studies are needed in non-corticosteroid maintenance, particularly looking into immunomodulators, biologics and probiotics.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Aditi Kumar: Data curation; Writing – original draft; Writing – review & editing.

George Hiner: Data curation; Writing – original draft; Writing – review & editing.

Matthew J. Brookes: Supervision; Validation; Writing – review & editing.

Jonathan P. Segal: Conceptualisation; Formal analysis; Funding acquisition; Methodology; Supervision; Validation; Writing – review & editing.

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Availability of data and materials
The datasets generated during and/or analysed during the current study are publicly available.

ORCID iD
Aditi Kumar https://orcid.org/0000-0003-1026-3173

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