AP&T Alimentary Pharmacology and Therapeutics

Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease

L. Moja*,†, S. Danese‡, G. Fiorino‡, C. Del Giovane§ & S. Bonovas*,¶

*Department of Biomedical Sciences for Health, University of Milan, Milan, Italy.
†Unit of Clinical Epidemiology, IRCCS Galeazzi Orthopedic Institute, Milan, Italy.
‡IBD Center, Department of Gastroenterology, IRCCS Humanitas Research Hospital, Milan, Italy.
§Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy.
¶Laboratory of Drug Regulatory Policies, IRCCS Mario Negri Institute for Pharmacological Research, Milan, Italy.

Correspondence to:
Dr S. Bonovas, Department of Biomedical Sciences for Health, University of Milan, Via Pascal 36, 20133 Milan, Italy.
E-mail: sbonovas@gmail.com

Publication data
Submitted 12 January 2015
First decision 29 January 2015
Resubmitted 17 March 2015
Accepted 17 March 2015
EV Pub Online 13 April 2015

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. This article was accepted for publication after full peer-review.

SUMMARY

Background
Budesonide and mesalazine (mesalamine) are commonly used in the medical management of patients with mild to moderate Crohn's disease.

Aim
To assess their comparative efficacy and harm using the methodology of network meta-analysis.

Methods
A comprehensive search of Medline, Embase, the Cochrane Library and ClinicalTrials.gov, through October 2014, was performed to identify randomised controlled trials (RCTs) that recruited adult patients with active or quiescent Crohn's disease, and compared budesonide or mesalazine with placebo, or against each other, or different dosing strategies of one drug.

Results
Twenty-five RCTs were combined using Bayesian network meta-analysis. Budesonide 9 mg/day, or at higher doses (15 or 18 mg/day), was shown superior to placebo for induction of remission [odds ratio (OR), 2.93; 95% credible interval (CrI), 1.52–5.39, and OR, 3.28; CrI, 1.46–7.55 respectively] and ranks at the top of the hierarchy of the competing treatments. For maintenance of remission, budesonide 6 mg/day demonstrated superiority over placebo (OR, 1.69; CrI, 1.05–2.75), being also at the best ranking position among all compared treatment strategies. No other comparisons (i.e. different doses of mesalazine vs. placebo or budesonide, for induction or maintenance of remission) reached significance. The occurrence of withdrawals due to adverse events was not shown different between budesonide, mesalazine and placebo, in both the induction and maintenance phases.

Conclusions
Budesonide, at the doses of 9 mg/day, or higher, for induction of remission in active mild or moderate Crohn's disease, and at 6 mg/day for maintenance of remission, appears to be the best treatment choice.

doi:10.1111/apt.13190

INTRODUCTION

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract characterised by transmural inflammation, a discontinuous pattern of distribution, a tendency to form fibrotic strictures and fistulas and periods of active disease alternating with periods of remission.[1, 2] Though typically involving distal ileum, ileocaecal region, colon and the perianal region, it can affect any part of the digestive tract. The causes of Crohn's disease are still uncertain, while its incidence and prevalence have increased in the past 50 years, up to 6–15 per 100 000 person-years and 50–200 per 100 000 persons, respectively.[3] The disease symptoms, including abdominal pain, diarrhoea, rectal bleeding, weight loss and loss of energy, as well as its intestinal and extra-intestinal complications, significantly affect patients' physical and psychosocial functioning.[4]

A variety of therapeutic agents are currently available in clinical practice to induce and maintain remission in Crohn's disease, including glucocorticoids, aminosalicylates, immunosuppressive agents and more recently biological therapies.[5, 6] Among them, budesonide, a glucocorticoid that has topical anti-inflammatory action with lower systemic activity than conventional glucocorticoids, and mesalazine (mesalamine), an aminosalicylate encapsulated for controlled gut release, are widely used as initial therapies for mild or moderate Crohn's disease. Budesonide appears more effective than placebo for induction of remission in active disease, mesalazine may not improve remission rates; both drugs may or may not maintain remission in quiescent disease.[7]

Structured evidence on comparative effectiveness and safety of budesonide and mesalazine would be very useful for patients and clinicians, as they are commonly used as alternative and interchangeable treatments. To address this issue, we conducted a systematic review of randomised controlled trials (RCTs) evaluating budesonide and mesalazine use in adults for induction of remission in active Crohn's disease or maintenance of remission. We assessed their comparative clinical efficacy and harm using the methodology of network meta-analysis, also known as multiple-treatments meta-analysis or mixed-treatment comparison[8, 9] that allows a unified and coherent synthesis of data from RCTs for comparisons of multiple treatments, while fully respecting randomisation. We aimed to provide a useful summary to support clinical decision-making, and explore future research needs (i.e. the justification for head-to-head trials comparing certain doses of budesonide vs. mesalazine).

METHODS

Protocol and registration

Our study protocol[10] is registered on PROSPERO: the international prospective register of systematic reviews. This work was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) recommendations.[11]

Data sources and searches

To identify the studies of interest, two independent investigators (LM and SB) systematically searched MEDLINE and EMBASE electronic databases from inception to 31 October 2014. Both Medical Subject Heading (MeSH) terms and free-text words were used, including the key words: *budesonide, mesalazine, mesalamine, pentasa, aminosalicylic acid, aminosalicylate, 5-aminosalicylic acid, 5-aminosalicylate, 5-ASA,* or *5ASA,* combined with *crohn disease, colitis, regional enteritis, ileitis* or *inflammatory bowel disease*. The search was limited to clinical trials and human studies. Language or age restrictions were not imposed. We searched the Cochrane Library for any RCT included in the Cochrane Central Register of Controlled Trials and for any systematic review that addressed a similar question. We finally explored the *ClinicalTrials.gov* website for completed but unpublished RCTs.

The title and abstract of studies identified were scanned to exclude any irrelevant publications. The full text of the selected articles was read to determine whether it contained information on the topic of interest. The bibliographies of the articles, and of reviews and meta-analyses, were scanned to identify other pertinent studies. We further asked field experts to provide additional references.

Selection criteria

Randomised controlled trials having enrolled adults (>90% of participants over the age of 18 years) with active mild or moderate Crohn's disease, or quiescent Crohn's disease, and comparing budesonide or mesalazine with placebo, or against each other (i.e. head-to-head trials), or different dosing strategies of one drug (dose-comparison studies) were considered eligible for inclusion. Studies had to report an assessment of induction of remission in active Crohn's disease, or of maintenance of remission in quiescent disease, using the Crohn's Disease Activity Index (CDAI),[12] another validated severity scale (e.g. Harvey Bradshaw Index),[13] or other author-defined criteria for remission.

Duration of therapy had to be at least 6 weeks for RCTs reporting induction of remission, and at least 6 months for trials reporting prevention of relapse. We considered only the maintenance studies of medically induced remission of Crohn's disease; studies of patients with surgically induced remission were excluded. RCTs were eligible for inclusion irrespective of country, or source of funding.

Data extraction and types of outcomes

Two reviewers (LM and SB) abstracted the data independently. The following information was collected from each study: (i) publication data: first author's last name, year of publication and geographical location of the study; (ii) study design and duration; (iii) number of participants; (iv) population and disease characteristics; (v) definition of remission/relapse; and (vi) interventions' parameters: drug, dosage and schedule. Differences in data extraction were resolved by consensus, referring back to the original article.

The primary efficacy outcomes were: the induction of remission in active Crohn's disease (at the last time-point assessment in the trial), and the maintenance of remission in quiescent disease (at 12 months, if available; otherwise at the last time-point assessment in the trial). The intention-to-treat principle was adopted: analysis was based on the total number of randomly assigned participants, irrespective of how the original study investigators analysed the data. All drop-outs were treated as treatment failures (i.e. failure to achieve remission in active Crohn's disease, and relapse in quiescent disease). We also studied the occurrence of adverse events (AEs) leading to premature drug discontinuation or withdrawal from the study, as safety endpoint.

It is possible that the relative efficacies of budesonide and mesalazine may depend on the dose used and, in particular, that higher doses are more effective. Therefore, different doses could not be ignored in the analysis, so that the same drug defines a single node in the network irrespective of the dose. We also tried to avoid extreme splitting (i.e. defining different nodes for each dose). As an alternative between these two extreme cases, we categorised the drug doses as follows: (i) For induction of remission in active Crohn's disease: budesonide <9 mg/day vs. 9 mg/day vs. >9 mg/day; mesalazine <2 g/day vs. 2–4 g/day vs. >4 g/day. (ii) For prevention of relapse in quiescent Crohn's disease: budesonide <6 mg/day vs. 6 mg/day vs. >6 mg/day; mesalazine <2 g/day vs. ≥2 g/day. The threshold choices were arbitrary.

Assessment of risk of bias in included studies

Reviewers assessed the risk of bias in the results of included studies by use of the Cochrane Collaboration's tool,[14] which addresses the following key domains: sequence generation; allocation concealment; blinding of participants and personnel; incomplete outcome data; selective outcome reporting; and other sources of bias. These items are considered as key domains for risk-of-bias assessment and classified as 'adequate' (low risk of bias), 'inadequate' (high risk of bias) or 'unclear'. Studies with adequate procedures in all six domains are considered to have a low risk of bias; ones with inadequate procedures in one or more domains are considered to have a high risk of bias; and those with unclear procedures in one or more domains are considered to have unclear risk of bias. In our assessment, disagreements among reviewers were discussed, and agreement was reached by consensus.

Data synthesis and analysis

We conducted the network meta-analysis within a Bayesian framework using Markov chain Monte Carlo (MCMC) methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[15] We adopted the random-effects rather than the fixed-effects model as the most appropriate and conservative approach to account for between-trial variability. Vague normal priors were placed on the study effects and a non-informative half-normal prior was placed on the common variance. A common heterogeneity standard deviation was assumed for each pairwise comparison. Posterior distributions were obtained after 3 000 000 iterations that followed 100 000 burn-in iterations. To ensure that we ended up with an independent sample from the posterior distributions of parameters of interest, we thinned out the resulting Markov chains by taking every 10th MCMC.[16] Convergence and lack of autocorrelation were checked and confirmed.

We estimated the posterior median odds ratios (ORs) and their 95% credible intervals (CrI), the Bayesian equivalent to confidence intervals, to assess treatment effects. Results for which the CrI of the OR did not include the unit value were regarded as significant. Given the results of the network meta-analysis, we calculated the surface under the cumulative ranking area (SUCRA),[17] which is used to provide a hierarchy of the treatments for each outcome. The larger the SUCRA value, the better the rank of the treatment (i.e. the more effective the treatment).

The estimate of common heterogeneity, mean tau, was used as a marker of between-trial heterogeneity. Potential

inconsistency, defined as the discrepancy of results across the direct and indirect evidence comparisons in closed loops, was also assessed. Inconsistency factors and their 95% CIs were calculated. The goodness-of-fit of the models was examined. A model is considered to provide an adequate fit to the data when the posterior mean residual deviance is similar to the number of data points used in the model.[18] Given that each pairwise comparison included a limited number of RCTs, we could not formally assess publication bias.

RESULTS

Search results

After duplicates' removal, the database search yielded 2023 literature citations (Figure 1, flow diagram). Records clearly not eligible or irrelevant to the topic were excluded. We retrieved 117 publications for detailed evaluation. The full text was read and the reference lists were checked. We initially identified 24 RCTs[19–42] eligible for inclusion in our systematic review. Of those, 22 studies had released their data in full-text publications,[19, 21–39, 41, 42] one in abstract form,[40] while we found the data for another unpublished RCT (Crohn's II study) within the results of a previous systematic review.[20] One additional eligible study[43] was identified through the *ClinicalTrials.gov* website, for a total of 25 trials.

A further five studies[44–48] included in a previous systematic review[20] did not meet our eligibility criteria. Two were excluded because patients were randomised during disease flare-up and not while in remission[44, 45]; one did not report rates of remission but rates of 'improvement',[46] one was neither randomised nor placebo-controlled[47] and another one was excluded because the drug dose was unclear.[48] Three more trials were also excluded from the analyses because the duration of therapy was short.[49–51] There was 100% agreement between reviewers regarding study selection.

The 25 studies selected for inclusion were two-arm (n = 18) or multi-arm (n = 7) RCTs, having enrolled adults with active (n = 11) or quiescent Crohn's disease (n = 14), and comparing budesonide (n = 8) or mesalazine (n = 12) with placebo or against each other (i.e. head-to-head trials; n = 3), or different doses of one drug (i.e. dose-comparison studies; n = 2). The majority of those trials (22 of 25) had used the CDAI to define remission. A summary of the trials' characteristics is shown in Tables S1 and S2 for induction and maintenance respectively.

Risk of bias in included studies

(i) *Allocation sequence*: twelve of 25 RCTs (48%) reported adequate methods for sequence generation and were judged to be at low risk of bias. Information in 13 trials (52%) was insufficient to permit judgement (i.e. unclear risk of bias).

(ii) *Allocation concealment*: eight of 25 RCTs (32%) reported adequate methods for allocation concealment (low risk of bias). However, for most of the trials (n = 17; 68%) information was insufficient (unclear risk).

(iii) *Blinding*: twenty-three of 25 RCTs (92%) were double-blind, one was investigator-blind (patients not blinded), and for another one information was insufficient.

(iv) *Incomplete outcome data*: fourteen of 25 RCTs (56%) were judged to be at high risk of bias. They reported high numbers of patients with unknown outcome, unequally balanced across intervention groups. Eight trials (32%) were judged to be at low risk, while for three (12%), information was insufficient.

(v) *Selective outcome reporting*: the majority of RCTs (n = 23; 92%) were at low risk of bias. Study protocols were not available but the published reports included all outcomes of interest for the review.

(vi) *Other sources of bias*: three studies (12%) suffered baseline imbalances across the intervention groups (high risk of bias), two were stopped early and another two did not provide information to assess whether an important problem exists (unclear risk).

Overall, the assessment indicated high risk of bias across 19 of the included studies (76%) and unclear risk for the other six (24%). None of the RCTs was judged to be at low risk of bias. Quality assessment items are summarised in Figure S1 for induction, and in Figure S2 for maintenance trials.

Results of multiple-treatments meta-analyses

Efficacy of budesonide and mesalazine for induction of remission. Seven two-arm[20, 21, 26, 27, 35, 42, 43] and four multi-arm studies[19, 24, 36, 37] comparing budesonide (n = 3) or mesalazine (n = 5) with placebo or against each other (n = 2), or different doses of one drug (n = 1) were included in the induction treatment network (Table S1 and Figure S3). In total, 1799 patients had been randomised to placebo (n = 355), budesonide (n = 757) or mesalazine (n = 687), in doses as in Table S1, as induction therapy (6–16 weeks) in active Crohn's disease. In 721 patients (40.1%), remission was induced.

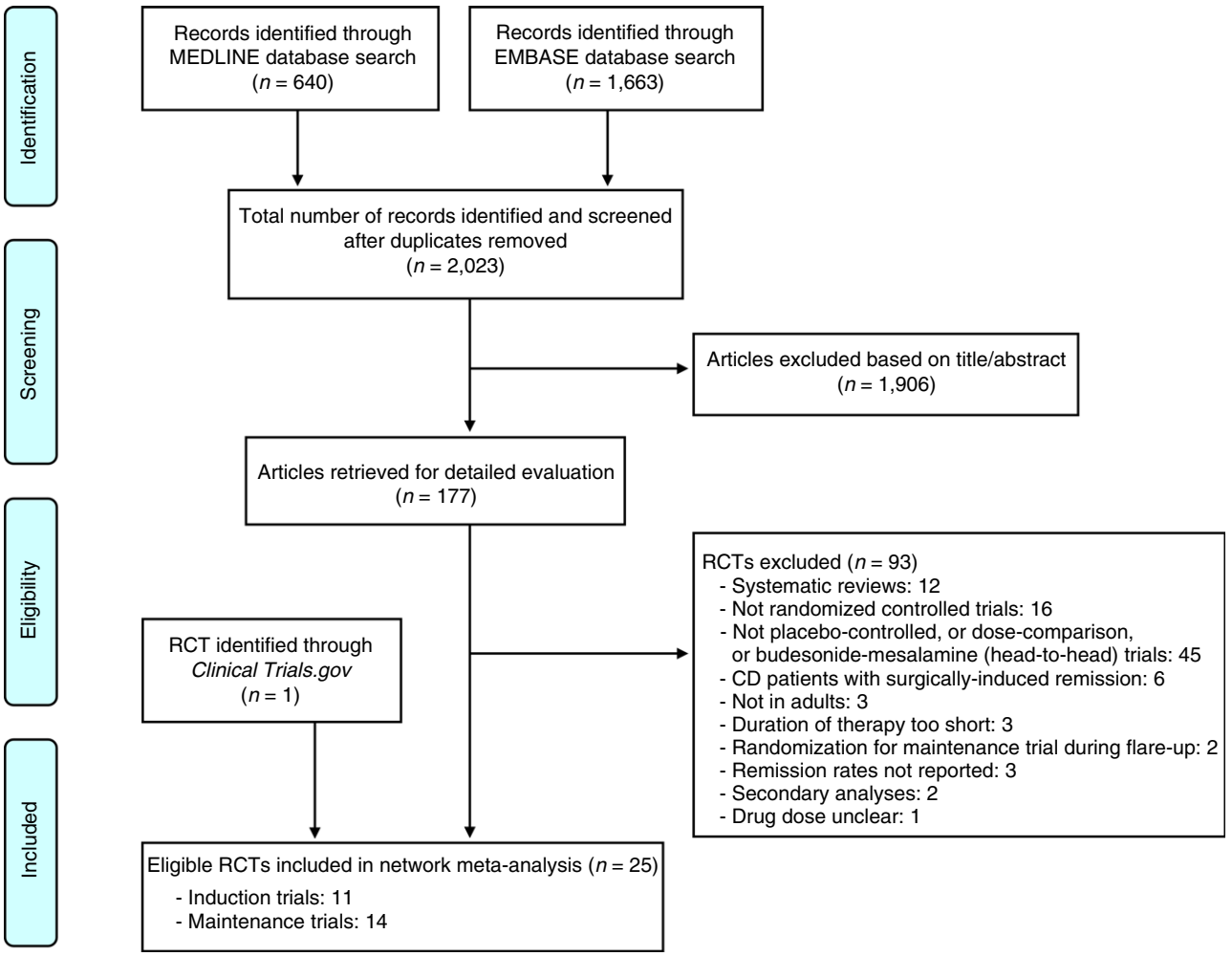

Figure 1 | Summary of evidence search and selection. RCT, randomised controlled trial; CD, Crohn's disease.

Only budesonide 9 mg/day (approved dose) or at higher doses (budesonide 15 or 18 mg/day) demonstrated superiority over placebo for induction of remission (OR = 2.93; 95% CrI: 1.52–5.39, and OR = 3.28; 95% CrI: 1.46–7.55 respectively). None of the other comparisons (i.e. different doses of mesalazine vs. placebo or budesonide) reached statistical significance. The posterior relative efficacy estimates for all comparisons (expressed as ORs) are shown in Table 1a.

In agreement, the corresponding SUCRA values (providing the hierarchy for the competing treatments) expressed as percentages were: 13% for placebo; 41% for budesonide 3 or 6 mg/day; 85% for budesonide 9 mg/day; 90% for budesonide 15 or 18 mg/day; 31% for mesalazine <2 g/day; 38% for mesalazine 2–4 g/day; and 53% for mesalazine >4 g/day.

Withdrawals due to AEs in induction trials. Nine RCTs[19, 21, 26, 27, 35–37, 42, 43] contributed to this analysis. They had randomised 1463 patients, of whom 121 (8.3%) withdrew due to AEs. Numbers were rather small for comparison of separate drug doses; thus, different doses were merged.

The occurrence of AEs leading to premature drug discontinuation or withdrawal from the induction trials was not shown statistically different between budesonide, mesalazine and placebo (Table 1b).

Surface under the cumulative ranking area values were: 68% for budesonide, 64% for placebo and 18% for mesalazine.

Efficacy of budesonide and mesalazine for maintenance of remission. Eleven two-arm[22, 23, 25, 28, 30, 33, 34, 38–41] and three multi-arm studies,[29, 31, 32] comparing budesonide (n = 5) or mesalazine (n = 7) with placebo or against each other (n = 1), or different doses of one drug (n = 1) were included in the maintenance treatment network (Table S2 and Figure S4). In total, 2147 patients

Table 1 | Induction therapy: treatment effect estimates from Bayesian network meta-analyses

(a) Efficacy of comparator treatments for induction of remission.

Mesalazine > 4.0 g/d						
1.35 (0.35–3.79)	Mesalazine 2.0 to 4.0 g/d					
1.50 (0.30–5.11)	1.11 (0.41–2.75)	Mesalazine < 2.0 g/d				
0.56 (0.15–1.64)	0.42 (0.16–1.11)	0.37 (0.12–1.32)	Budesonide 15 or 18 mg/d			
0.63 (0.21–1.48)	0.47 (0.23–1.06)	0.42 (0.16–1.35)	1.13 (0.55–2.43)	Budesonide 9 mg/d		
1.25 (0.32–3.93)	0.92 (0.34–2.74)	0.83 (0.25–3.24)	2.23 (0.96–5.40)	1.98 (0.86–4.52)	Budesonide 3 or 6 mg/d	
1.84 (0.55–4.80)	1.37 (0.75–2.65)	1.23 (0.53–3.28)	**3.28 (1.46–7.55)**	**2.93 (1.52–5.39)**	1.48 (0.58–3.66)	Placebo

(b) Withdrawals due to adverse events in induction trials.

Mesalazine		
1.45 (0.60–3.24)	Budesonide	
1.40 (0.63–3.29)	0.97 (0.44–2.27)	Placebo

The column-defining treatment is compared with the row-defining treatment. The estimates in the cells are odds ratios with 95% credible intervals. Statistically significant results are shown in bold.

had been randomised to placebo (n = 937), budesonide (n = 505) or mesalazine (n = 705), in doses as in Table S2, as maintenance therapy (median duration: 12 months) in quiescent Crohn's disease. Of them, 1002 patients (46.7%) maintained remission.

Only budesonide 6 mg/day demonstrated superiority over placebo for maintenance of remission (OR = 1.69; 95% CrI: 1.05–2.75). None of the other comparisons (i.e. different doses of mesalazine vs. placebo or budesonide) reached statistical significance. The posterior relative efficacy estimates for all comparisons are shown in Table 2a.

In agreement, the corresponding SUCRA values (providing the hierarchy for the competing treatments) were: 16% for placebo; 39% for budesonide 3 mg/day; 80% for budesonide 6 mg/day; 79% for budesonide 9 mg/day; 54% for mesalazine <2 g/day; and 32% for mesalazine ≥2 g/day.

Withdrawals due to AEs in maintenance trials. Thirteen RCTs[23, 25, 28–34, 38–41] contributed to this analysis. They had randomised 1990 patients, of whom 166 (8.3%) withdrew due to AEs. Once again, numbers were small for comparison of separate drug doses; thus, different doses were merged.

The occurrence of AEs leading to premature drug discontinuation or withdrawal from the maintenance trials was not shown statistically different between budesonide, mesalazine and placebo (Table 2b). SUCRA values were: 68% for budesonide, 64% for placebo and 18% for mesalazine.

Evaluation of heterogeneity, consistency and overall fit of the models. Heterogeneity among trials was low to moderate for all the outcomes (Table 3). Moreover, there was no evidence of substantial inconsistency between direct and indirect comparisons in closed loops (Table S3). However, given the relatively low number of studies, relevant inconsistency or heterogeneity between trials cannot be ruled out. Evaluation of the goodness-of-fit for the models showed adequate fit for all analyses (Table 3).

DISCUSSION

In this systematic review and Bayesian network meta-analysis, we incorporated 25 RCTs comparing budesonide or mesalazine with placebo or against each other, or different dosing strategies of one drug, for the management of adult patients with active or quiescent Crohn's disease. Meta-analysis of the induction studies showed that budesonide 9 mg/day or at higher doses (15 or 18 mg/day) is superior to placebo, and ranks at the top of the hierarchy of the competing treatments. For maintenance of remission, only budesonide 6 mg/day

Table 2 | Maintenance therapy: treatment effect estimates from Bayesian network meta-analyses

(a) Efficacy of comparator treatments for maintenance of remission.

Mesalazine ≥ 2.0 g/d					
0.83 (0.41–1.58)	Mesalazine < 2.0 g/d				
0.59 (0.22–1.56)	0.71 (0.24–2.22)	Budesonide 9 mg/d			
0.65 (0.37–1.12)	0.78 (0.38–1.71)	1.10 (0.49–2.49)	Budesonide 6 mg/d		
0.94 (0.51–1.71)	1.14 (0.53–2.56)	1.60 (0.58–4.38)	1.45 (0.82–2.61)	Budesonide 3 mg/d	
1.10 (0.79–1.51)	1.33 (0.75–2.45)	1.86 (0.72–4.77)	**1.69 (1.05–2.75)**	1.17 (0.69–1.96)	Placebo

(b) Withdrawals due to adverse events in maintenance trials.

Mesalazine		
1.71 (0.67–4.71)	Budesonide	
1.19 (0.72–1.99)	0.70 (0.30–1.56)	Placebo

The column-defining treatment is compared with the row-defining treatment. The estimates in the cells are odds ratios with 95% credible intervals. Statistically significant results are shown in bold.

Table 3 | Between trial heterogeneity and evaluation of model fit

Outcome	Mean tau	Number of data points	Residual deviance
Induction of remission	0.42	27	26.74
Withdrawals due to AEs in induction trials	0.32	18	14.22
Maintenance of remission	0.16	31	29.87
Withdrawals due to AEs in maintenance trials	0.22	26	22.53

The model is considered to provide an adequate fit to the data if the mean of the residual deviance is similar to the number of data points used in the model.

demonstrated superiority over placebo, being also at the best ranking position among all compared treatment strategies. None of the other comparisons (i.e. different doses of mesalazine vs. placebo or budesonide, for induction or maintenance of remission) reached statistical significance. On the other hand, the occurrence of withdrawals due to AEs was not shown different between budesonide, mesalazine and placebo, in both the induction and maintenance phases.

Previous pairwise meta-analyses have indicated a benefit of budesonide over placebo in active Crohn's disease remission,[52, 53] but – contrary to our findings – no benefit in preventing quiescent disease relapse.[52, 54] Similar to our results, they found no evidence to suggest that mesalazine is superior to placebo for induction[20, 55] or maintenance of remission[20, 56] in patients with Crohn's disease. Our network meta-analysis includes not only the results of direct comparisons but also incorporates indirect comparisons, particularly for budesonide vs. mesalazine, which have been rarely compared in head-to-head trials. Thus, our study uses a much broader evidence base and includes a large number of trials, providing updated evidence that can be more appropriately integrated into relevant clinical guidelines.

Our work brings new evidence into the field for several reasons. Having conducted a rigorous and extensive literature search, we are confident that all relevant RCTs have been properly identified. Different doses of the same treatment were treated as separate interventions – a fact that reduces conceptual heterogeneity. The outcome data were extracted with a rigorous definition of remission, using the CDAI, which has been applied in the majority of the included RCTs. There was no evidence of substantial inconsistency; heterogeneity among trials was found to be from low to moderate; and the models showed adequate fit to the data.

Nevertheless, our analysis has several limitations. Firstly, all the RCTs included in our review were characterised by high or unclear risk of bias, as assessed with the Cochrane Collaboration's tool. This is a fact of concern, as the quality of the current analysis is limited by the quality of the underlying data. Secondly, most studies included within the network meta-analysis were placebo-controlled trials, with only three head-to-head trials, and two studies comparing different dosing strategies. Thirdly, because the exposure and follow-up times lasted up to 1 year, estimates of comparative effectiveness corresponding to longer periods are not possible. Fourthly, we could not assess publication bias. Fifthly, we did not evaluate comparator treatments in terms of cost, which is a key consideration in clinical decision-making. Sixthly, we did not evaluate different release mechanisms of mesalazine, depending on disease localisation, and this could be a key aspect due to the multiple anatomical patterns of the disease. Finally, our systematic review does not cover the whole 5-ASA drug class, but is restricted to mesalazine. In fact, this network meta-analysis was originally planned to explore the value of doing further head-to-head trials comparing budesonide vs. mesalazine. To make sure that a new clinical trial is justifiable, both scientifically and ethically, it should be designed in the light of an assessment of relevant previous research, as recommended.[57]

It is also important to note that in a network meta-analysis of RCTs, the value of randomisation does not hold across trials. Hence, a network meta-analysis is a form of observational evidence,[58, 59] and may be biased if differences in unmeasured covariates among the original studies act as effect modifiers of relative treatment effects. Given the temporal variation (year of publication ranging from 1987 to 2013) and the geographic representation (Tables S1 and S2), important differences between patient populations (e.g. differences in history of treatment) may exist. For this reason, it remains important that further studies – high-quality trials as well as studies in the 'real world' setting – are conducted to confirm and extend our findings. This is particularly true when grouping patients with mild or moderate Crohn's disease, as the efficacy of budesonide or mesalazine could be different in mild as compared to moderate disease. Finally, although our network meta-analysis demonstrated superiority of budesonide 6 mg/day over placebo for maintenance of remission, it is possible that this benefit may be inconsistent over time. Our literature-based analysis, which evaluated maintenance of remission in quiescent disease at 12 months, could not answer this crucial question. Only an individual data-based analysis could eventually resolve this issue, but such an approach is not feasible, as most of the trials have been conducted during the 1990s and their data are inaccessible.

Despite these limitations, this network meta-analysis provides the largest scale comparative evidence on the profiles of budesonide and mesalazine for the treatment of Crohn's disease. According to our study findings, budesonide (at the doses of 9 mg/day, or higher, for induction of remission in active mild or moderate Crohn's disease, and at 6 mg/day for maintenance of remission) appears to be the best treatment choice.

This evidence, along with the treatment costs, patient's values and preferences, and other factors such as the risks of budesonide treatment in the long term in relation to steroid side effects, and the potential of 5-ASA therapy to reduce colorectal cancer risk,[60] should be considered to inform clinical decision-making.[61] Nevertheless, further high-quality research – ensuring clear definitions of remission, defining the proper patient population (e.g. mild or moderate), rigorous collection of AE data and complete follow-up of patients – is welcome, and may be necessary to extend the current evidence and assess the long-term efficacy and safety profiles of alternative therapies for Crohn's disease.

AUTHORSHIP

Guarantor of the article: Dr Stefanos Bonovas.

Author contributions: L. Moja, S. Danese, G. Fiorino, C. Del Giovane, S. Bonovas: conception and design. S. Danese: obtaining funding, L. Moja, S. Bonovas: literature search and data collection. C. Del Giovane, S. Bonovas: statistical analysis. L. Moja, S. Danese, G. Fiorino, C. Del Giovane, S. Bonovas: data interpretation. S. Bonovas: drafting of the manuscript. L. Moja, S. Danese, G. Fiorino, C. Del Giovane, S. Bonovas: critical revision of the manuscript for important intellectual content. L. Moja, S. Danese, G. Fiorino, C. Del Giovane, S. Bonovas: final approval of the version to be published, including the authorship list. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal interests: Silvio Danese has served as a speaker, consultant and advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson & Johnson. Gionata Fiorino has received consulting fees from Abbott Immunology, MSD and Janssen Pharmaceuticals. All the other

authors report no conflict of interest related to the present article.

Declaration of funding interests: This study was funded by the Centro Ricerca e Cura delle Malattie Infiammatorie Croniche Intestinali, IRCCS Istituto Clinico Humanitas; and the Fondazione Italiana per la Ricerca Sulle Malattie Apparato Digerente (FIRMAD). The funding sources had no role in the design of the study; the collection, analysis, and interpretation of the data; and the decision to approve publication of the finished manuscript.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Summary of risk-of-bias assessments for 'induction' RCTs.

Figure S2. Summary of risk-of-bias assessments for 'maintenance' RCTs.

Figure S3. Network geometry for induction treatment. Network geometry of randomised controlled trials (RCTs) evaluating budesonide and/or mesalazine for induction of remission in adult patients with active Crohn's disease. Nodes represent certain drug doses; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison, also represented by the numbers.

Figure S4. Network geometry for maintenance treatment. Network geometry of randomised controlled trials (RCTs) evaluating budesonide and/or mesalazine for maintenance of remission in adult patients with quiescent Crohn's disease. Nodes represent certain drug doses; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison, also represented by the numbers.

Table S1. Randomized controlled trials included in the 'induction treatment' network.

Table S2. Randomized controlled trials included in the 'maintenance treatment' network.

Table S3. Evaluation of consistency.

REFERENCES

1. Jewell DP. Crohn's disease. In: Warrell DA, Cox TM, Firth JD, Benz EJ, eds. *Oxford Textbook of Medicine*, 4th ed. Oxford: Oxford University Press, 2005.
2. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathological clinical entity. *JAMA* 1932; **99**: 1323–9.
3. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785–94.
4. Akobeng AK. Review article: the evidence base for interventions used to maintain remission in Crohn's disease. *Aliment Pharmacol Ther* 2008; **27**: 11–8.
5. Dignass A, Van Assche G, Lindsay JO, *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010; **4**: 28–62.
6. Stidham RW, Lee TC, Higgins PD, *et al.* Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2014; **39**: 1349–62.
7. Farrell RJ, Peppercorn MA. Overview of the medical management of mild to moderate Crohn's disease in adults. UpToDate website. Available at: http://www.uptodate.com/contents/overview-of-the-medical-management-of-mild-to-moderate-crohns-disease-in-adults?source=search_result&search=management+of+crohn%27s+disease&selectedTitle=1%7E150 (accessed 27 March 2015).
8. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ* 2013; **346**: f2914.
9. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331**: 897–900.
10. Danese S, Fiorino G, Del Giovane C, Moja L, Bonovas S. Comparative efficacy and safety of budesonide and mesalamine for Crohn's disease: a systematic review and network meta-analysis of randomized controlled trials. PROSPERO 2014:CRD42014009300. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009300 (accessed 27 March 2015).
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**: 264–9 W64.
12. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**: 439–44.
13. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. *Lancet* 1980; **1**: 514.
14. Higgins JP, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
15. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000; **10**: 325–37.
16. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998; **7**: 434–55.
17. 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.
18. Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med* 2006; **166**: 1269–75.
19. Suzuki Y, Motoya S, Takazoe M, *et al.* Efficacy and tolerability of oral budesonide in Japanese patients with

active Crohn's disease: a multicentre, double-blind, randomized, parallel-group Phase II study. *J Crohns Colitis* 2013; **7**: 239–47.
20. Ford AC, Kane SV, Khan KJ, *et al.* Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 617–29.
21. Tromm A, Bunganic I, Tomsová E, *et al.* Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011; **140**: 425–34 e1.
22. de Jong DJ, Bac DJ, Tan G, *et al.* Maintenance treatment with budesonide 6 mg versus 9 mg once daily in patients with Crohn's disease in remission. *Neth J Med* 2007; **65**: 339–45.
23. Hanauer S, Sandborn WJ, Persson A, Persson T. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. *Aliment Pharmacol Ther* 2005; **21**: 363–71.
24. Herfarth H, Gross V, Andus T, *et al.* Analysis of the therapeutic efficacy of different doses of budesonide in patients with active Crohn's ileocolitis depending on disease activity and localization. *Int J Colorectal Dis* 2004; **19**: 147–52.
25. Mantzaris GJ, Petraki K, Sfakianakis M, *et al.* Budesonide versus mesalamine for maintaining remission in patients refusing other immunomodulators for steroid-dependent Crohn's disease. *Clin Gastroenterol Hepatol* 2003; **1**: 122–8.
26. Tremaine WJ, Hanauer SB, Katz S, *et al.* Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002; **97**: 1748–54.
27. Thomsen OO, Cortot A, Jewell D, *et al.* A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998; **339**: 370–4.
28. Gross V, Andus T, Ecker KW, *et al.* Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. The Budesonide Study Group. *Gut* 1998; **42**: 493–6.
29. Ferguson A, Campieri M, Doe W, Persson T, Nygård G. Oral budesonide as maintenance therapy in Crohn's disease – results of a 12-month study. Global Budesonide Study Group. *Aliment Pharmacol Ther* 1998; **12**: 175–83.
30. Sutherland LR, Martin F, Bailey RJ, *et al.* A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1997; **112**: 1069–77.
31. Löfberg R, Rutgeerts P, Malchow H, *et al.* Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. *Gut* 1996; **39**: 82–6.
32. Greenberg GR, Feagan BG, Martin F, *et al.* Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. *Gastroenterology* 1996; **110**: 45–51.
33. Thomson AB, Wright JP, Vatn M, *et al.* Mesalazine (Mesasal/Claversal) 1.5 g b.d. vs. placebo in the maintenance of remission of patients with Crohn's disease. *Aliment Pharmacol Ther* 1995; **9**: 673–83.
34. Arber N, Odes HS, Fireman Z, *et al.* A controlled double blind multicenter study of the effectiveness of 5-aminosalicylic acid in patients with Crohn's disease in remission. *J Clin Gastroenterol* 1995; **20**: 203–6.
35. Tremaine WJ, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994; **19**: 278–82.
36. Greenberg GR, Feagan BG, Martin F, *et al.* Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* 1994; **331**: 836–41.
37. Singleton JW, Hanauer SB, Gitnick GL, *et al.* Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993; **104**: 1293–301.
38. Gendre JP, Mary JY, Florent C, *et al.* Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID). *Gastroenterology* 1993; **104**: 435–9.
39. Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. The Italian IBD Study Group. *Gastroenterology* 1992; **103**: 363–8.
40. Bondesen S, the Danish 5-ASA Group. Mesalazine (Pentasa) as prophylaxis in Crohn's disease. A multicenter, controlled trial. *Scand J Gastroenterol* 1991; **26**(Suppl. 183): F44.
41. International Mesalazine Study Group. Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. *Aliment Pharmacol Ther* 1990; **4**: 55–64.
42. Rasmussen SN, Lauritsen K, Tage-Jensen U, *et al.* 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. *Scand J Gastroenterol* 1987; **22**: 877–83.
43. A study with pentasa in patients with active crohn's disease (PEACE). Available at: http://clinicaltrials.gov/show/NCT00862121 (accessed 27 March 2015)
44. de Franchis R, Omodei P, Ranzi T, *et al.* Controlled trial of oral 5-aminosalicylic acid for the prevention of early relapse in Crohn's disease. *Aliment Pharmacol Ther* 1997; **11**: 845–52.
45. Modigliani R, Colombel JF, Dupas JL, *et al.* Mesalamine in Crohn's disease with steroid-induced remission: effect on steroid withdrawal and remission maintenance, Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* 1996; **110**: 688–93.
46. Mahida YR, Jewell DP. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. *Digestion* 1990; **45**: 88–92.
47. Bresci G, Parisi G, Banti S. Long-term therapy with 5-aminosalicylic acid in Crohn's disease: is it useful? Our four years experience. *Int J Clin Pharmacol Res* 1994; **14**: 133–8.
48. Wellmann W, Schroder U. New oral preparations for maintenance therapy in Crohn's disease. *Can J Gastroenterol* 1988; **2**(Suppl. A): 71A–2A.
49. Brignola C, Iannone P, Pasquali S, *et al.* Placebo-controlled trial of oral 5-ASA in relapse prevention of Crohn's disease. *Dig Dis Sci* 1992; **37**: 29–32.
50. Cortot A, Colombel JF, Rutgeerts P, *et al.* Switch from systemic steroids to budesonide in steroid dependent patients with inactive Crohn's disease. *Gut* 2001; **48**: 186–90.
51. Saverymuttu SH, Gupta S, Keshavarzian A, Donovan B, Hodgson HJ. Effect of a slow-release 5'-aminosalicylic acid preparation on disease activity in Crohn's disease. *Digestion* 1986; **33**: 89–91.
52. Ford AC, Bernstein CN, Khan KJ, *et al.* Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 590–9.

53. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008; CD000296.
54. Kuenzig ME, Rezaie A, Seow C, *et al.* Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014; **8**: CD002913.
55. Lim WC, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2010; CD008870.
56. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Cochrane Database Syst Rev* 2005; CD003715.
57. Clarke M. Doing new research? Don't forget the old *PLoS Med* 2004; **1**: e35.
58. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; **159**: 130–7.
59. Wells G, Sultan S, Chen L, Khan M, Coyle D. *Indirect Evidence: Indirect Treatment Comparisons in Meta-analysis*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2009.
60. Lopez A, Peyrin-Biroulet L. 5-Aminosalicylic acid and chemoprevention: does it work? *Dig Dis* 2013; **31**: 248–53.
61. Schoepfer AM, Bortolotti M, Pittet V, *et al.* The gap between scientific evidence and clinical practice: 5-aminosalicylates are frequently used for the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2014; **40**: 930–7.