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SYSTEMATIC REVIEW AND META–ANALYSIS

Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: Systematic review and network meta-analysis

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AIMS

Oral systemic corticosteroids have been used to induce remission in patients with active inflammatory bowel disease (IBD) for over 50 years; however, the wide array of adverse events (AEs) associated with these drugs prompted the development of steroid compounds with targeted delivery and low systemic bioavailability. This study assessed corticosteroids' comparative harm using network meta-analysis.

METHODS

We searched PubMed, Scopus, Embase, the Cochrane Library, clinical trial registries, regulatory authorities' websites and major conference proceedings, through March 2017. Randomized controlled trials that recruited adult IBD patients and compared oral systemic corticosteroids (prednisone/prednisolone) or compounds/formulations with low systemic bioavailability (budesonide, budesonide MMX, and beclomethasone dipropionate) with placebo, or against each other, were considered eligible for inclusion. Two reviewers independently extracted study data and outcomes, and rated each trial's risk-of-bias.

RESULTS

We identified and synthesized evidence from 31 trials including 5689 IBD patients. Budesonide MMX was associated with significantly fewer corticosteroid-related AEs than oral systemic corticosteroids [odds ratio (OR): 0.25, 95% confidence interval (CI): 0.13–0.49] and beclomethasone (OR: 0.35, 95% CI: 0.13–1.00), but not significantly fewer AEs than budesonide (OR: 0.64, 95% CI: 0.37–1.11); it performed equally good with placebo. By contrast, the occurrence of serious AEs, and treatment discontinuations due to AEs, did not differ between the comparator treatments.

CONCLUSIONS

Budesonide MMX is associated with fewer corticosteroid-related AEs than its comparator steroid treatments for adult IBD patients. Further high-quality research is warranted to illuminate the steroid drugs' comparative safety profiles.

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBDs) with a remitting and relapsing clinical course and unclear aetiology. They require long-lasting treatment targeting both flare-up periods and maintenance of remission [1, 2]. A variety of therapeutic agents are currently available in IBD clinical practice, including glucocorticosteroids.

Oral systemic steroids (**prednisone**, **prednisolone**) have been used to induce remission in patients with active IBD for over 50 years due to their potent anti-inflammatory effects [3]. However, the plethora of adverse effects associated with these drugs due to their systemic metabolism, including ophthalmic (cataracts and glaucoma), skin, metabolic (from an altered fat distribution to diabetes mellitus), gastrointestinal, musculoskeletal (from osteopenia to osteoporosis) and central nervous system effects, as well as hypertension, adrenal suppression and opportunistic infections [4, 5], has prompted the development of less toxic steroid compounds. Currently, topically acting oral steroids (**budesonide** and **beclomethasone dipropionate**), which are characterized by a high topical anti-inflammatory activity and a low systemic bioavailability, represent an important weapon in the IBD armamentarium [6]. Moreover, a novel oral formulation of budesonide, which uses the Multi-Matrix System (MMX) technology for delivering drugs to the colon (budesonide MMX), has been developed [7].

Given the widespread use of the different steroids in IBD clinical practice, structured evidence on comparative safety of systemic and topically acting (low-bioavailability) steroids would be very useful for patients and clinicians. To address this issue, we conducted a systematic review of randomized controlled trials (RCTs) evaluating corticosteroid use in IBD adults. We assessed their comparative harm using the methodology of network meta-analysis, also known as multiple-treatments meta-analysis or mixed-treatment comparison [8–10], which allows a unified and coherent synthesis of data from RCTs for simultaneous comparison of multiple interventions, while respecting randomization. We aimed to provide a clinically useful summary of the existing evidence to assist physicians in the decision-making process.

Methods

Protocol and registration

Our study protocol [11] is registered with the International Prospective Register of Systematic Reviews (PROSPERO – http://www.crd.york.ac.uk/prospero). The current systematic review was performed in accordance with the Cochrane Handbook [12], the ISPOR network meta-analysis guidance [13, 14], and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [15].

Data sources and search strategy

We systematically searched the PubMed, Scopus and Embase bibliographic databases from their inception to 31 March 2017 (date of final search). Search algorithms included the following terms: *prednisone*, *prednisolone*, *budesonide* or *beclomethasone*, combined with *Crohn's disease*, *ulcerative colitis* or *inflammatory bowel disease*. The search was limited to clinical trials. Language restrictions were not imposed.

We also searched the Cochrane Library for any relevant RCT included in the IBD Group Specialized Trials Register, and for any systematic review that addressed a similar question; the WHO International Clinical Trials Registry Platform, and the http://clinicaltrials.gov to ensure identification of all trials; and major international conference proceedings (European Crohn's and Colitis Organisation, 2011–2016; Digestive Disease Week, 2011–2016; and the United European Gastroenterology Week, 2011–2016).

Two authors (S.B. and T.L.) independently reviewed titles and abstracts; the full texts of the selected articles were critically examined for eligibility; and their reference lists (and those of relevant systematic reviews and meta-analyses in the discipline) were searched to identify further eligible trials. Finally, we conducted supplemental searches of regulatory authorities' websites (www.fda.gov, www.ema.europa.eu and www.tga.gov.au) to identify drug assessment reports including data of completed but unpublished studies.

Selection criteria

Parallel-group RCTs having enrolled adult patients (>90% of participants over the age of 18 years) with IBD (either CD or UC), and comparing systemic corticosteroid drugs (prednisone, prednisolone) or compounds/formulations with low systemic bioavailability (budesonide, budesonide MMX, beclomethasone dipropionate) with placebo, or against each other (i.e. head-to-head trials), were eligible for inclusion. Studies evaluating multi-interventional therapies, in which the effect of the steroid treatment could be separated from that of other treatments, were also considered eligible.

If the results of a study were reported at multiple time-points, we included those corresponding to the longest duration, provided it remained a randomized trial and fully reported the outcomes of interest. Studies were excluded if they were observational; examined topical corticosteroids (e.g. suppositories, enemas, foam preparations) or drugs not commonly used in practice (e.g. betamethasone phosphate, fluticasone propionate); did not investigate patients with CD or UC (i.e. trials in lymphocytic colitis were excluded); evaluated different dosages of one drug (i.e. dose-comparison studies) without another active drug or placebo as a control arm; did not report (or provided insufficient data for) the outcomes of interest; or were conducted in paediatric populations. No restrictions were applied by drug dose, or length of follow-up.

Data extraction and quality assessment

Two reviewers (S.B. and T.L.) independently abstracted the following data from each study in a form: first author, journal and year of publication, study design and duration, number of participants, underlying condition, patient characteristics (age, sex and concomitant treatments), interventions (drug and dosage), and number of patients with events reported for the intervention and control group. Study results posted at http://clinicaltrials.gov were also checked.

Any discrepancies were resolved via consensus referring back to the original article.

Different doses were treated as the same intervention (i.e. they define a single node in the network).

The estimated measures of effect were the odds ratios (ORs) for the following adverse outcomes:

(i) number of treatment discontinuations or withdrawals from the study due to adverse events (AEs);
(ii) number of patients with any (one or more) serious AEs (SAEs), which are defined as any untoward medical occurrence that results in death, requires hospital admission or prolongation of existing hospital stay, causes persistent or significant disability/incapacity, or is life threatening [16];
(iii) number of patients with corticosteroid-related AEs (i.e. the occurrence of one or more of the following symptoms: moon face, buffalo hump, acne, hirsutism, purple skin striae, easy bruising, ankle swelling, hair loss, mood swings, depression, sleep changes and insomnia).

Analysis was based on the total number of randomly assigned patients (intention-to-treat principle), wherever trial reporting allowed this (if not applicable, then all evaluable patients).

We assessed risk of bias (RoB) in included studies using the Cochrane Collaboration's tool [17, 18].

For methodological details see Appendix (Risk of bias assessment: Methods).

Data synthesis and analysis

We conducted the network meta-analysis within a frequentist framework in STATA (Stata Corp., College Station, TX, USA) using the network suite [19] and other network-related commands [20, 21].

Data were analysed in two formats: In the augmented format, all treatments were compared with a reference group (placebo), and studies without the reference arm were augmented with an artificial placebo group including a small amount of data [19, 22, 23]. In the standard format, each study had its own reference group. Results using the two formats were almost identical. Unless stated otherwise, results are from analyses on data in the augmented format. When no events occurred in one group of a trial, we used a continuity correction inversely proportional to the relative size of the opposite group. In particular, the continuity correction for the treatment group was $1/(R + 1)$, where R is the ratio of control group to treatment group sizes. Similarly, the continuity correction for the control group was $R/(R + 1)$. This approach outperforms the use of a constant continuity correction of 0.5 in settings of sparse event data and imbalanced study groups [24]. Trials reporting zero-event data for both study groups were not included in the analyses.

Multivariate random-effects meta-analyses were fit to model the intervention effects across studies using consistency and inconsistency models [19, 22, 23, 25, 26]. The off-diagonal cells of the league tables contain odds ratios and 95% confidence intervals from all pairwise comparisons in network meta-analyses. The contribution of direct evidence to the mixed estimates and the entire network was also calculated and plotted [20, 27]. Probabilities of each treatment being at a specific order, mean ranks of treatments, and surface under the cumulative ranking area (SUCRA) values [19, 20, 28], were estimated running 10 000 replications. SUCRA is used to provide a hierarchy of treatments for each outcome. The larger the SUCRA value, the better (i.e. the safer) the treatment.

To assess the comparative safety profiles distinguishing short-term from long-term side effects, subgroup analyses were also performed according to study duration; a cut-off of 12 weeks was used.

Heterogeneity (within each comparison) was estimated through the restricted maximum likelihood approach, and was assumed to be constant across treatment contrasts (common τ^2) [19, 23]. Predictive intervals that reflect the extent of heterogeneity in network meta-analytic effect estimates, and in which future relative treatment effects are expected to lie, were estimated and plotted [20, 21]. Cochran Q test for heterogeneity, I^2 and τ^2 for all direct comparisons were computed. The magnitude of τ^2 estimated in every direct synthesis of evidence was compared to quantiles of empirical distributions found in meta-analyses [27, 29].

For the inconsistency models, the design-by-treatment interaction approach was used [23, 25, 30]. Inconsistency terms were modelled as fixed parameters. Global Wald tests for inconsistency were performed that jointly examine the inconsistency parameters [23, 25]. Inconsistency was also explored by node-splitting using the symmetrical option [25, 31], and by calculating the inconsistency factor between direct and indirect evidence in all closed loops (triangular and quadratic) in the networks [20, 27, 32]. Inconsistency factor is the ratio of the direct and indirect ORs in each loop.

Selective outcome reporting or publication bias was assessed by inspecting funnel plots appropriately adjusted for the inclusion of studies that compare different pairs of treatments [20, 21, 33]. Comparisons were consistently defined across studies focusing on active drugs *vs*. placebo. In the absence of small-study effects, the plot should be symmetric around the zero line.

Results

Search results

After removal of duplicates, the database search yielded 1552 literature citations (Figure 1, flow chart). Records clearly not eligible or irrelevant to the topic were excluded. We retrieved 97 publications for detailed evaluation. The full text was read, and the bibliographies were checked. We initially identified 27 RCTs eligible for inclusion in the Network [34–59]. Four additional eligible studies were identified in regulatory authorities' drug assessment reports [60, 61], for a total of 31 trials (Table 1).

A total of 5689 adults were randomized (CD, n = 3608; UC, n = 2081). Mean age of participants ranged between 30 and 44 years, females between 40% and 55%, and follow-up times from 1 to 24 months. The total period of observation was over 40 000 person-months (7 months per patient, on average) with a high number of AEs; 378 patients

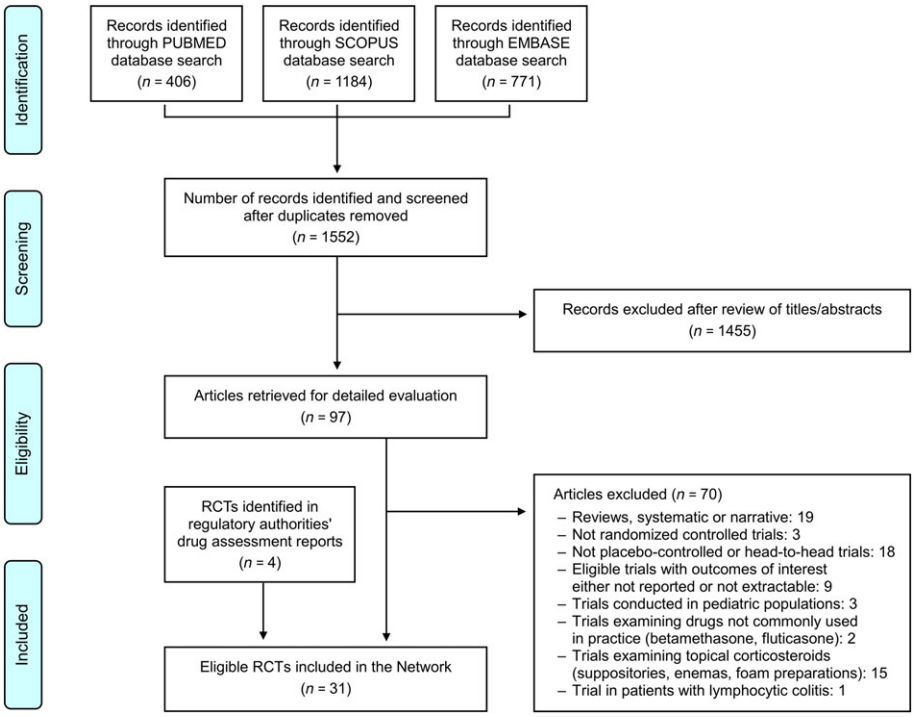

Figure 1

Summary of the evidence search and selection process (flow chart). RCTs, randomized controlled trials

discontinued treatment or withdrew from study due to AEs, 210 patients had one or more SAEs, and 1061 patients had one or more corticosteroid-related AEs. Publication dates ranged from 1979 to 2017. A summary of trials' characteristics is given in Table 1.

The RoB assessment indicated low RoB in two studies (6%), which had short duration and reported high rates of complete follow-up without other threats to validity. 21 trials (68%) were rated as high-risk, while RoB was unclear for the remaining eight (26%). For details see Appendix (Risk of bias assessment: Results). The quality assessment items (per trial) are shown in Figure 2.

Results of network meta-analyses

Treatment discontinuations or withdrawals from the studies due to AEs. Twenty-seven RCTs [34, 36–52, 54–56, 58–61] comparing budesonide to placebo (n = 13), budesonide MMX to placebo (n = 5), prednisone/prednisolone to placebo (n = 2), beclomethasone dipropionate to placebo (n = 2), budesonide to budesonide MMX (n = 1), prednisone/prednisolone to budesonide (n = 5), and prednisone/prednisolone to beclomethasone dipropionate (n = 1) were analysed (Table 1, and Figure 3A).

A total of 5158 patients had been randomized to placebo (n = 1572), budesonide (n = 1714), budesonide MMX (n = 876), prednisone/prednisolone (n = 764) and beclomethasone dipropionate (n = 232). Of them, 378 patients (7.3%) discontinued treatment or withdrew from the studies due to AEs.

In the network meta-analysis, none of the comparisons among the competing treatments was statistically significant (Table 2A). By contrast, the SUCRA values, the mean ranks and the estimated probabilities of each treatment being the best demonstrated a trend favouring beclomethasone dipropionate (Table 3A).

SAEs. Twenty RCTs [34, 37, 38, 41, 44–46, 50–56, 58–61] comparing budesonide to placebo (n = 9), budesonide MMX to placebo (n = 5), prednisone/prednisolone to placebo (n = 2), budesonide to budesonide MMX (n = 1), prednisone/prednisolone to budesonide (n = 4), and prednisone/prednisolone to beclomethasone dipropionate (n = 1), were incorporated in the analysis (Table 1, and Figure 3B).

In total, 4178 patients had been randomized to placebo (n = 1209), budesonide (n = 1304), budesonide MMX (n = 876), prednisone/prednisolone (n = 652) and beclomethasone dipropionate (n = 137). Overall, 210 patients (5.0%) suffered SAEs.

In network meta-analysis, none of the comparisons among the treatments was statistically significant (Table 2 B). Similarly, the corresponding SUCRA values, the estimated probabilities of each treatment being the best, as well as the comparative treatment ranks, were inconclusive (Table 3B).

Corticosteroid-related AEs. Twenty-six RCTs [34, 35, 37–40, 42–46, 48, 50–61] comparing budesonide to placebo (n = 11), budesonide MMX to placebo (n = 5), prednisone/prednisolone to placebo (n = 2), beclomethasone to placebo (n = 1), budesonide to budesonide MMX (n = 1), budesonide to prednisone/prednisolone (n = 6), beclomethasone to prednisone/prednisolone (n = 1), and

Table 1

Characteristics of the randomized controlled trials included in the network

Study [reference]	Condition	Study groups, intervention parameters, patients randomized	Duration (weeks)	Mean age (years)	Women (%)
Bar-Meir *et al.*, 1998 [34]	CD	Budesonide 9 mg day^{-1} (n = 100) Prednisone 40 mg day^{-1} tapered gradually to 5 mg day^{-1} (n = 101)	8	32.8	48.3
Campieri *et al.*, 1997 [35]	CD	Budesonide 9 mg day^{-1} tapered to 6 mg day^{-1} after 8 weeks, and to 3 mg day^{-1} after a further 2 weeks (n = 119) Prednisolone 40 mg day^{-1} tapered to 30 mg day^{-1} after 2 weeks, and then continuously throughout the study, reaching 5 mg day^{-1} after 9 weeks (n = 58)	12	36.7	59.3
Cortot *et al.*, 2001 [36]	CD	Budesonide 6 mg day^{-1} (n = 60) Placebo (n = 60)	13	33.5	59.0
Ewe *et al.*, 1999 [37]	CD	Budesonide 3 mg day^{-1} (n = 43) Placebo (n = 40)	52	34.0	55.4
Ferguson *et al.*, 1998 [38]	CD	Budesonide 6 mg day^{-1}, or 3 mg day^{-1} (n = 48) Placebo (n = 27)	52	35.9	54.7
Greenberg *et al.*, 1996 [39]	CD	Budesonide 6 mg day^{-1}, or 3 mg day^{-1} (n = 69) Placebo (n = 36)	52	35.6	60.0
Greenberg *et al.*, 1994 [40]	CD	Budesonide 15 mg day^{-1}, 9 mg day^{-1}, or 3 mg day^{-1} (n = 192) Placebo (n = 66)	8	NR	62.4
Gross *et al.*, 1998 [41]	CD	Budesonide 3 mg day^{-1} (n = 84) Placebo (n = 95)	52	32.0	59.2
Gross *et al.*, 1996 [42]	CD	Budesonide 9 mg day^{-1} (n = 34) M-Prednisolone 48 mg day^{-1} tapered gradually to 8 mg day^{-1} (n = 33)	8	31.0	58.2
Hanauer *et al.*, 2005 [43]	CD	Budesonide 6 mg day^{-1} (n = 55) Placebo (n = 55)	52	40.4	62.7
Hellers *et al.*, 1999 [44]	CD	Budesonide 6 mg day^{-1} (n = 63) Placebo (n = 67)	52	35.0	51.9
Löfberg, Danielsson *et al.*, 1996 [45]	UC	Budesonide 10 mg day^{-1} tapered gradually to 4 mg day^{-1} (n = 34) Prednisolone 40 mg day^{-1} tapered gradually to 5 mg day^{-1} (n = 38)	9	33.5	41.7
Löfberg, Rutgeerts *et al.*, 1996 [46]	CD	Budesonide 6 mg day^{-1}, or 3 mg day^{-1} (n = 63) Placebo (n = 27)	52	35.0	60.0
Malchow *et al.*, 1984 (ECCDS) [47]	CD	M-Prednisolone 48 mg day^{-1} tapered gradually to 12 mg day^{-1} (active disease), or 8 mg day^{-1} (quiescent disease) (n = 113) Placebo (n = 110)	104	29.9	54.7
Malchow *et al.*, 1984 (ECCDS) [47]	CD	M-Prednisolone 48 mg day^{-1} tapered gradually to 12 mg day^{-1} (active disease), or 8 mg day^{-1} (quiescent disease) + sulfasalazine 3 g day^{-1} (n = 112) Placebo + sulfasalazine 3 g day^{-1} (n = 117)	104	30.9	54.6
Prantera *et al.*, 2011 [48]	CD	Beclomethasone dipropionate 15 mg day^{-1} for 2 weeks, and then 10 mg day^{-1} for 22 weeks (n = 37) Placebo (n = 36)	24	42.4	53.4
Rizzello *et al.*, 2002 [49]	UC	Beclomethasone dipropionate 5 mg day^{-1} +5-ASA 3.2 g day^{-1} (n = 58) Placebo +5-ASA 3.2 g day^{-1} (n = 61)	4	43.9	29.4
Rutgeerts *et al.*, 1994 [50]	CD	Budesonide 9 mg day^{-1} for 8 weeks, and then 6 mg day^{-1} for 2 weeks (n = 88) Prednisolone 40 mg day^{-1} for 2 weeks, then gradually reduced to 5 mg day^{-1} (n = 88)	10	35.5	61.9
Sandborn *et al.*, 2012 (CORE I) [51]	UC	Budesonide MMX 9 mg day^{-1}, or 6 mg day^{-1} (n = 255) Placebo (n = 128)	8	42.2	44.1
Schoon *et al.*, 2005 [52]	CD	Budesonide 9 mg day^{-1}; dose could be adjusted by clinicians (n = 138) Prednisolone 40 mg day^{-1}; dose could be adjusted by clinicians (n = 134)	104	36.9	51.3

(*continues*)

Table 1

(Continued)

Study [reference]	Condition	Study groups, intervention parameters, patients randomized	Duration (weeks)	Mean age (years)	Women (%)
Singleton *et al.*, 1979 (NCCDS: part I, phase 1) [53]	CD	Prednisone 0.25–0.75 mg kg^{-1} daily; maximum daily dose was 60 mg (n = 85) Placebo (n = 77)	17	32.7	50.6
Singleton *et al.*, 1979 (NCCDS: part II) [53]	CD	Prednisone 0.25 mg kg^{-1} daily; maximum daily dose was 20 mg (n = 61) Placebo (n = 101)	104	32.0	47.5
Suzuki *et al.*, 2013 [54]	CD	Budesonide 15 mg day^{-1}, or 9 mg day^{-1} (n = 51) Placebo (n = 26)	8	36.5	28.6
Travis *et al.*, 2014 (CORE II) [55]	UC	Budesonide MMX 9 mg day^{-1}, or 6 mg day^{-1} (n = 254) Budesonide 9 mg day^{-1} (n = 126) Placebo (n = 128)	8	38.0	45.2
Tremaine *et al.*, 2002 [56]	CD	Budesonide 9 mg day^{-1} (n = 159) Placebo (n = 41)	8	39.4	64.0
Tursi *et al.*, 2006 [57]	CD	Budesonide 9 mg day^{-1} (n = 15) Beclomethasone dipropionate 10 mg day^{-1} (n = 15)	8	33.4	56.7
Van Assche *et al.*, 2015 [58]	UC	Beclomethasone dipropionate 5 mg day^{-1} for 4 weeks, followed by 5 mg every other day for the further 4 weeks (n = 137) Prednisone 40 mg day^{-1} for 2 weeks, tapered of 10 mg every 2 weeks during the 8-week study period (n = 145)	8	NR	40.4
Rubin *et al.*, 2017 [59]	UC	Budesonide MMX 9 mg day^{-1} as add-on to existing 5-ASA therapy (n = 255) Placebo as add-on to existing 5-ASA therapy (n = 255)	8	44.5	46.0
BUC-16/CDA [60]	CD	Budesonide 18 mg day^{-1}, 9 mg day^{-1}, or 3 mg day^{-1}, followed by a dose reduction period of 2 weeks (n = 307) Placebo (n = 102)	10	NR	NR
CB-01-02/05 & CRO-03-53-period 1 [61]	UC	Budesonide MMX 9 mg day^{-1}, or 3 mg day^{-1} (n = 50) Placebo (n = 35)	4–8	NR	NR
CB-01-02/04 [61]	UC	Budesonide MMX 6 mg day^{-1} (n = 62) Placebo (n = 60)	52	NR	NR

CD, Crohn's disease; UC, ulcerative colitis

budesonide to beclomethasone (n = 1) were analysed (Table 1, and Figure 3C).

A total of 4819 patients had been randomized to placebo (n = 1307), budesonide (n = 1704), budesonide MMX (n = 876), prednisone/prednisolone (n = 743) and beclomethasone dipropionate (n = 189). Of them, 1061 patients (22.0%) suffered corticosteroid-related AEs.

In the network meta-analysis, budesonide MMX was associated with statistically significantly fewer corticosteroid-related AEs than prednisone/prednisolone (OR: 0.25, 95% CI: 0.13–0.49) and beclomethasone dipropionate (OR: 0.35, 95% CI: 0.13–1.00), but not significantly fewer corticosteroid-related AEs than budesonide (OR: 0.64, 95% CI: 0.37–1.11); it performed equally good with placebo (Table 2C). All other treatments were significantly less safe than placebo (Table 2C), and budesonide was better than prednisone/prednisolone (OR: 0.39, 95% CI: 0.27–0.57).

In agreement, the SUCRA values providing the hierarchy of the treatments, the estimated probabilities of each treatment being the best, and the ranking of the treatments with regards to the occurrence of corticosteroid-related AEs, demonstrated budesonide MMX ranking at the top among its comparator treatments (Table 3C).

Assessment of publication bias, homogeneity and consistency of the models. The inspection of funnel plots appropriately adjusted for inclusion of studies comparing different treatments against placebo (Figure S1) suggested a low probability of publication bias or selective outcome reporting, for any of the models.

The conventional statistics (Cochran Q, I^2, τ^2) calculated for all direct comparisons, and the estimated and plotted predictive intervals reflecting the extent of heterogeneity in network meta-analytic estimates, indicated low to moderate heterogeneity for all outcomes (data not shown). This was confirmed by the overall network heterogeneity variance (τ^2) estimates (Table 4).

Finally, there was no evidence of substantial inconsistency when explored either by node splitting, or by calculating the difference between direct and indirect evidence in all closed loops in the networks (data not shown). The

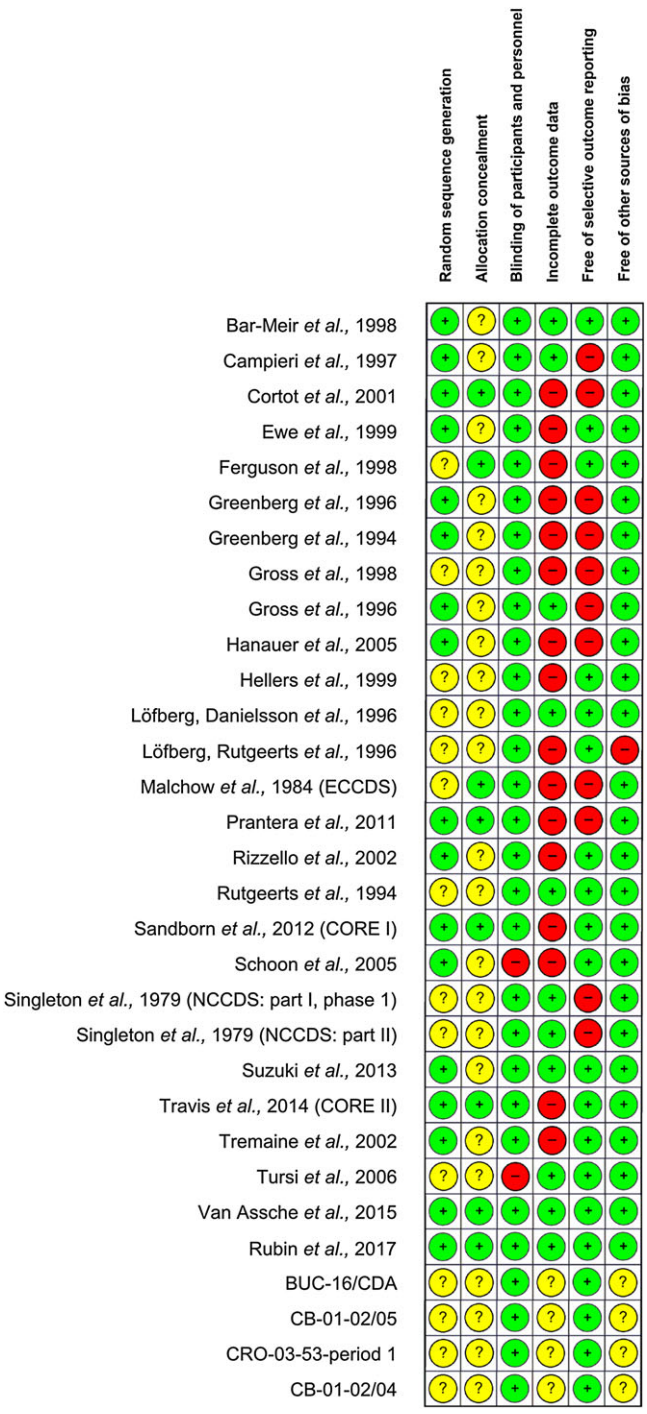

Figure 2

Risk of bias assessment for the studies included in the network. Green (+), low risk of bias; yellow (?), unclear risk of bias; red (–), high risk of bias

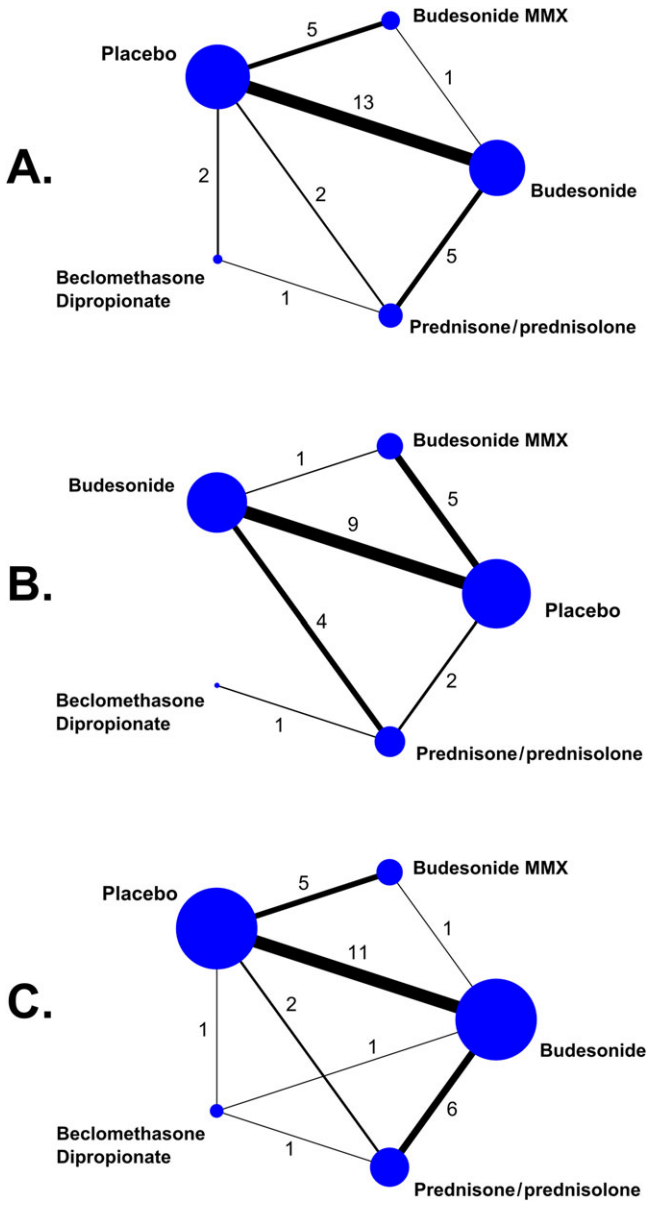

Figure 3

Network geometry. The nodes represent the individual drugs; lines represent direct comparisons using clinical trials; thickness of lines represents the number of available clinical trials, also represented by the numbers. (A) Treatment discontinuation or withdrawal from the study due to adverse events. (B) Serious adverse events. (C) Corticosteroid-related adverse events

global Wald tests for inconsistency were not significant (Table 4).

Nevertheless, given the moderate number of studies included in the analyses, relevant inconsistency or heterogeneity between trials cannot be ruled out.

Additional analyses. To assess the comparative safety profiles distinguishing the short-term from the long-term side effects, we also performed subgroup analyses using a cut-off of 12 weeks for separating studies of short duration (up to 12 weeks) [34, 35, 40, 42, 45, 49–51, 54–61] from those of long duration (over 12 weeks) [36–39, 41, 43, 44, 46–48, 52, 53, 61] (Table 1).

Again, the occurrence of SAEs, and the occurrence of treatment discontinuations due to AEs, did not differ between the comparator treatments, both in the short and

Table 2

Assessment of comparative safety of systemic and low-bioavailability corticosteroids in inflammatory bowel diseases

A. Treatment discontinuations or withdrawals from the study due to adverse events				
PBO				
1.07 (0.73–1.55)	***B-MMX***			
0.93 (0.64–1.35)	0.87 (0.54–1.41)	**BUD**		
1.88 (0.67–5.26)	1.76 (0.59–5.24)	2.03 (0.70–5.90)	***BDP***	
1.03 (0.53–1.98)	0.96 (0.46–2.02)	1.11 (0.57–2.15)	0.55 (0.19–1.56)	**PRED**
B. Serious adverse events				
PBO				
0.73 (0.36–1.50)	***B-MMX***			
0.94 (0.56–1.59)	1.29 (0.54–3.06)	**BUD**		
0.30 (0.01–8.29)	0.42 (0.01–12.1)	0.32 (0.01–8.46)	***BDP***	
1.01 (0.53–1.94)	1.38 (0.53–3.57)	1.07 (0.69–1.65)	3.32 (0.13–84.9)	**PRED**
C. Corticosteroid-related adverse events				
PBO				
1.02 (0.64–1.64)	***B-MMX***			
0.65 (0.47–0.92)	0.64 (0.37–1.11)	**BUD**		
0.36 (0.14–0.93)	**0.35 (0.13–1.00)**	0.55 (0.23–1.35)	**BDP**	
0.26 (0.16–0.42)	**0.25 (0.13–0.49)**	**0.39 (0.27–0.57)**	0.71 (0.31–1.66)	***PRED***

The column-defining treatment is compared with the row-defining treatment. The effect estimates in the cells are odds ratios (with 95% confidence intervals) from network meta-analysis. Because the outcomes are negative, ORs lower than 1.0 favour the treatment in the left upper square. Statistically significant results are shown in bold.
BDP, beclomethasone dipropionate; BUD, budesonide; B-MMX, budesonide MMX; IBD, inflammatory bowel disease; PBO, placebo; PRED, prednisone/prednisolone.

long term. Regarding the corticosteroid-related AEs, the SUCRA values providing the hierarchy of treatments, the estimated probabilities of each treatment being the best, and the ranking of the treatments, demonstrated budesonide MMX ranking at the top among comparator treatments, both in the short and long term. Moreover, the direction of the pairwise effect estimates was in agreement with the overall analysis; however, the statistical power was rather low, and few comparisons reached statistical significance.

The results of subgroup analyses are detailed in the Appendix (short-term group: Tables S1, S2, S3; long-term group: Tables S4, S5, S6).

Discussion

In this systematic review and network meta-analysis, we included safety data from 31 trials comparing oral systemic steroid drugs (prednisone, prednisolone) or steroids with low systemic bioavailability (budesonide, budesonide MMX, beclomethasone) with placebo, or against each other. We found that budesonide MMX is associated with significantly fewer corticosteroid-related AEs than oral systemic steroids and beclomethasone, but not significantly fewer events than budesonide; it performs equally good with placebo. By contrast, the occurrence of serious AEs, and treatment discontinuations due to AEs, were not shown to be different between the comparator steroid treatments.

Previous works [62–70] have examined the corticosteroid treatments' safety profiles in a conventional, pairwise manner. Our network meta-analysis includes not only the results of direct comparisons but also incorporates indirect comparisons, such as for budesonide MMX *vs*. oral systemic steroids or budesonide MMX *vs*. beclomethasone dipropionate, which have never been compared head-to-head. Thus, our study uses a much broader base of research data and provides new comparative evidence that can be appropriately integrated into relevant clinical practice guidelines.

Our work has merits: a rigorous and extensive search was conducted to retrieve all eligible studies, data were extracted by two independent reviewers with any disagreements checked and resolved, studies were analysed on an intention-to-treat basis, and appropriate frequentist methodology was employed to synthesize the evidence, also accounting for sparse data and imbalanced study groups. Finally, there was no evidence of substantial inconsistency,

Table 3

Assessment of comparative safety of systemic and low-bioavailability corticosteroids in inflammatory bowel diseases

	SUCRA value (%)	Probability best (%)	Mean rank
A. Treatment discontinuations or withdrawals from the study due to adverse events			
PBO	40.2	2.3	3.4
B-MMX	*51.4*	9.8	2.9
BUD	27.6	2.3	3.9
BDP	*87.4*	*77.7*	*1.5*
PRED	43.5	7.9	3.3
B. Serious adverse events			
PBO	66.1	27.7	2.4
B-MMX	*35.7*	10.1	3.6
BUD	56.7	12.0	2.7
BDP	*25.5*	*20.6*	*4.0*
PRED	66.0	29.6	2.4
C. Corticosteroid-related adverse events			
PBO	85.8	44.4	1.6
B-MMX	*86.6*	54.2	1.5
BUD	48.9	0.2	3.0
BDP	*23.1*	*1.3*	*4.1*
PRED	5.6	0.0	4.8

Herein we present the SUCRA values providing the hierarchy of the competing treatments, the estimated probabilities of each treatment being the best, and the mean ranking of each treatment using 10 000 draws.
BDP, beclomethasone dipropionate; BUD, budesonide; B-MMX, budesonide MMX; IBD, inflammatory bowel disease; PBO, placebo; PRED, prednisone/prednisolone.

Table 4

Networks' assessment for homogeneity and consistency

Outcome	Heterogeneity variance	Global Wald test for inconsistency
Drug discontinuations or withdrawals due to AEs	$\tau^2 = 0.21$	*P*-value = 0.14
Serious AEs	$\tau^2 < 0.01$	*P*-value = 0.17
Corticosteroid-related AEs	$\tau^2 = 0.30$	*P*-value = 0.80

AEs, adverse events.

heterogeneity between studies was low to moderate and the probability of selective outcome reporting or publication bias was low.

Nevertheless, the strengths of this systematic review should be weighed against some limitations. First, the majority of the trials included in our meta-analysis were judged to be at high or unclear RoB, as assessed with the Cochrane's Collaboration tool; this is a fact of concern because the quality of the current analysis may be limited by the quality of primary data. Second, many studies were registration trials for regulatory purposes; as such, they have enrolled selective IBD populations (e.g. elderly and high-risk patients are under-represented). This is a limitation that might compromise external validity. Moreover, we did not evaluate the comparator treatments in terms of efficacy and cost, which are key considerations in the clinical decision-making process. Finally, the additional limitations of network meta-analysis should be acknowledged [71]. In a network meta-analysis of RCTs, the value of randomization does not hold across studies. Hence, a network meta-analysis of RCTs is a form of observational evidence: results and conclusions may be undermined if

extensive clinical and/or methodological heterogeneity is present. For example, differences among the trials regarding treatment history, ascertainment bias arising from frequency of follow-up visits, or the geographic regions where the studies were conducted (reflecting differences between patient populations) might act as effect modifiers. For all these reasons, it remains important that further high-quality research (head-to-head trials, real-world studies, pharmacoeconomic evaluations) is conducted in IBD to confirm and extend the current evidence, and illuminate the steroid treatments' comparative profiles.

Conclusion

Our meta-analysis synthesized data from a large number of RCTs and brings new evidence into the field with practical implications. Budesonide MMX has an advantage over oral systemic steroids and beclomethasone dipropionate for corticosteroid-related AEs (non-serious and not leading to drug withdrawal), and possibly a slight unconfirmed advantage over standard budesonide for these AEs.

This knowledge together with other important considerations, such as treatments' comparative efficacy and cost, will assist patients and physicians to make evidence-based decisions that align with their values, preferences, and tolerance of risks and benefits.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [72], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [73].

Competing Interests

Dr Gionata Fiorino has served as a consultant and advisory board member for MSD, AbbVie, Takeda, Pfizer, Mundipharma, Nikkiso, Otsuka. Prof Laurent Peyrin-Biroulet has received consulting fees from Abbvie, Amgen, Biogaran, Biogen, Boerhinger-Ingelheim, Bristol–Myers Squibb, Celgene, Celltrion, Ferring, Forward Pharma, Genentech, H. A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Lycera, Merck, Lilly, Mitsubishi, Norgine, Pfizer, Pharmacosmos, Pilège, Samsung Bioepis, Sandoz, Takeda, Therakos, Tillots, UCB Pharma and Vifor, and lecture fees from Abbvie, Ferring, H.A.C. Pharma, Janssen, Merck, Mitsubishi, Norgine, Takeda, Therakos, Tillots and Vifor. Prof Silvio Danese has served as a speaker, a consultant and an advisory board member for Abbvie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Sandoz, Tigenix, UCB Pharma and Vifor. All other authors have no conflicts of interest to declare.

Contributors

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Conception and design: All authors; Literature search and data collection: S.B., T.L. Statistical analysis: S.B., G.N; Data interpretation: All authors; Drafting of the manuscript: S.B., G.N; Critical revision of the manuscript for important intellectual content: All authors; Final approval of the version to be published: All authors; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13456/suppinfo

Figure S1 Funnel plots adjusted for inclusion of trials comparing different treatments against placebo
Table S1 Safety assessment of systemic and low-bioavailability steroids in inflammatory bowel disease: short-term group
Table S2 Safety assessment of systemic and low-bioavailability steroids in inflammatory bowel disease: short-term group
Table S3 Networks' assessment for homogeneity and consistency: short-term group
Table S4 Safety assessment of systemic and low-bioavailability steroids in inflammatory bowel disease: long-term group
Table S5 Safety assessment of systemic and low-bioavailability steroids in inflammatory bowel disease: long-term group
Table S6 Networks' assessment for homogeneity and consistency: long-term group