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Traditional corticosteroids for induction of remission in Crohn's disease (Review)

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Traditional corticosteroids for induction of remission in Crohn's disease.
Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792.
DOI: 10.1002/14651858.CD006792.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Traditional corticosteroids for induction of remission in Crohn's disease

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Editorial group: Cochrane IBD Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2010.

Citation: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2.

ABSTRACT

Background

Historically, corticosteroids have been the most commonly used class of medication for induction of remission in Crohn's disease (CD). Corticosteroids down regulate production of inflammatory cytokines and interfere with NF-κB production, thereby blunting inflammatory response.

Objectives

The primary objective was to systematically review the efficacy and safety of traditional corticosteroids (given orally or intravenously) for induction of remission in CD.

Search methods

The following electronic databases were searched: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD) Group Specialized Trial Register, and Clinical-Trials.gov. No language restrictions were applied. Reference lists of trials and review articles, as well as recent proceedings from major gastroenterology meetings were manually searched.

Selection criteria

Randomized, controlled clinical trials of traditional, systemic corticosteroids for the induction of remission of active CD were included in this review. Control groups included patients receiving either placebo or 5-aminosalicylates (5-ASA). The study population included patients of any age with active CD (as defined by the study authors or validated clinical activity indices), receiving any formulation of systemically available corticosteroid by any oral or parenteral methods of delivery. The primary outcome was induction of remission of CD. Secondary outcomes included clinical response, change in mean CDAI, adverse events and the proportion of patients withdrawing due to adverse events.

Data collection and analysis

Two independent investigators reviewed studies for eligibility, extracted the data and assessed study quality using Jadad's criteria. A random or fixed effects model was chosen based on an assessment of heterogeneity, and studies were weighted using the DerSimonian & Laird or the Mantel-Haenszel method accordingly. Meta-analysis was performed using RevMan 4.2.10 software.

Main results

Two studies compared corticosteroids to placebo and six studies compared corticosteroids to 5-ASA. Corticosteroids were found to be significantly more effective than placebo at inducing remission in CD (RR 1.99; 95% CI 1.51 to 2.64; P < 0.00001). Corticosteroids were found to be more effective than 5-ASA at inducing remission in studies with long follow-up duration (i.e. > 15 weeks; RR 1.65; 95% CI 1.33 to 2.03; P < 0.00001). Corticosteroids induced adverse events in a higher proportion of patients than placebo (RR 4.89; 95% CI 1.98 to 12.07; P = 0.0006), or low-dose 5-ASA (RR 2.38; 95% CI 1.34 to 4.25; P = 0.003). No difference existed in the proportion of patients experiencing adverse events when steroids were compared to high-dose 5-ASA. Steroids did not induce more study withdrawals due to adverse events than either placebo or 5-ASA.

Authors' conclusions

Corticosteroids are effective for induction of remission in patients with CD, particularly when used for more than 15 weeks. Although corticosteroids cause more adverse events than either placebo or low-dose 5-ASA, these adverse events did not lead to increased study withdrawal in the included studies. Further information is required to determine the optimal duration of treatment and tapering protocol to maximize the efficacy of treatment with corticosteroids. Additionally, further study is required to determine whether corticosteroids are more effective in patients with certain phenotypes or when administered intravenously.

PLAIN LANGUAGE SUMMARY

Corticosteroids for induction of remission in Crohn's disease

Corticosteroids have been used for decades to treat active Crohn's disease. Controlled clinical studies that evaluated the effect of systemic corticosteroids to induce remission in Crohn's disease were reviewed. For inclusion in this analysis, studies could compare any form of corticosteroid that is systemically absorbed (e.g. prednisone, prednisolone, 6-methylprednisolone or hydrocortisone) to either placebo (fake medicine) or 5-aminosalicylates (e.g. mesalazine, mesalamine or sulfasalazine). Corticosteroids were found to be more effective than either placebo or 5-aminosalicylates at inducing remission in Crohn's disease. Although corticosteroids caused side effects more often in patients compared with placebo and 5-aminosalicylates, these side effects were not serious enough to cause withdrawal from the studies reviewed. In summary, corticosteroids are effective at inducing remission in patients with Crohn's disease. While they cause frequent side effects, these side effects were relatively minor in the reviewed studies, some of which followed patients for up to 24 weeks.

BACKGROUND

Crohn's disease (CD) is characterized by chronic transmural inflammation of the gastrointestinal tract (Bousvaros 2007). A wide range of clinical symptoms occur with some patients remaining chronically clinically active and others experiencing a series of relapses and remissions. CD is currently thought to be caused by a cascade of immunologic reaction triggered by environmental factors in a genetically-predisposed host. Historically, prior to the advent of biologic therapies, corticosteroids had been the most effective class of medication for treatment of acute flares of CD in adults (Baumgart 2007) and children (Hyams 2005). Corticosteroids down regulate production of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-alpha by inhibiting transcription of specific genes involved in their production (Hyams 2000). Corticosteroids also inhibit protein synthesis by affecting the stability of messenger RNA (Barnes 1993). The interaction between corticosteroid receptors and NF-B results in down regulation of NF-B and therefore a blunting of inflammatory response (Yang 2002). Corticosteroids have been used for the treatment of inflammatory bowel disease (IBD) since the 1950s (Truelove 1954). Unfortunately, systemically available corticosteroids are associated with adverse effects such as moon facies, acne, infection (increased risk of abdominal and pelvic abscess in CD patients), ecchymoses, hypertension, diabetes mellitus, osteoporosis, cataracts, glaucoma and growth failure in children (Baumgart 2007).

More recently, topically-active formulations of corticosteroids (such as budesonide) have been developed in order to reduce systemic availability and adverse events while maintaining efficacy. Studies examining these non-traditional corticosteroids have been subject to previous meta-analysis (Otley 2005) and will therefore

not be included in this review.

Aminosalicylates and Crohn's disease

Another mainstay medication used for the past forty years in the treatment of CD are the 5-aminosalicylate (5-ASA) drugs, including sulfasalazine (Akobeng 2005). 5-ASA drugs act through a variety of mechanisms including inhibition of the NF-B pathway, inhibition of apoptosis induced by oxidative stress, modulation of prostaglandin metabolism, and inhibition of colonic production of leukotrienes (Desreumaux 2006). Although considered to be modestly effective at best for induction of remission in CD, 5-ASA drugs are used by many practitioners. One systematic review examined both placebo-controlled and corticosteroid-controlled clinical trials and concluded that 5-ASA was less effective for induction of remission than corticosteroids in patients with CD (Feagan 1998). A number of forms of 5-ASA have been developed for the treatment of IBD. Sulfasalazine, the earliest 5-ASA-containing drug, maintains its bond between sulphapyridine and 5-ASA until interacting with bacteria in the colon, where the bond is cleaved, releasing the 5-ASA moiety (Azad Khan 1977). One gram of sulfasalazine is reported to contain 400 mg of 5-ASA (Sandborn 2003). Other forms of 5-ASA such as mesalazine/mesalamine (Asacol®, Salofalk®, Rowasa®) are formulated to release according to the pH environment in the intestine and should be available in the distal ileum as well as the colon (Desreumaux 2006). By contrast, Pentasa® (mesalamine) was formulated for timed-release throughout the small intestine and colon (Hardy 1993). The choice of 5-ASA formulation is left to the individual practitioner, who must base the choice on CD location, previous experience, patient response and adverse effect profile. The effectiveness of 5-ASA for the treatment of active CD has been controversial. A recent meta-analysis of controlled clinical trials which included unpublished studies from the pharmaceutical industry has shown the limited efficacy of 5-ASA compared with placebo (Hanauer 2004). The continued debate potentially stems from differing study designs, the varying efficacy of different formulations and the possibility of better efficacy in colonic inflammation (Hanauer 2005; Kamm 2005; Stange 2005).

Importance of this review

Although a number of systematic reviews examine the efficacy of corticosteroids for induction of remission in CD (Yang 2002; Bebb 2004; Lichtenstein 2006), only one meta-analysis has been published (Salomon 1992). No studies have compared corticosteroids to 5-ASA using meta-analytic techniques. Despite the high incidence of adverse effects, oral and intravenous corticosteroids continue to be commonly used to induce clinical remission in active CD. Additionally, corticosteroids have been considered standard treatment in both clinical practice (Lichtenstein 2006) and recent randomized-controlled clinical trials involving patients with CD (Kamm 2006). It is important to carefully examine the efficacy and safety of corticosteroids, in order to provide an evidence-based approach to assessment of the risk/benefit profile of this class of medication.

OBJECTIVES

The primary objective was to systematically review the efficacy of traditional (systemically-absorbed, non-topical) corticosteroids for induction of remission in CD. The secondary objective was to evaluate adverse events associated with the use of corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled trials of oral or intravenous corticosteroids, administered for the induction of remission of CD in adults or children, published in any language, were included. Studies published in abstract form only were included if enough data were provided to assess outcome. The control arm of studies assessed must have included either placebo, 5-ASA or sulfasalazine. Studies with other medications in their control arms were not included to avoid overlap with previously published meta-analyses.

Types of participants

Participants included patients of any age with CD defined by conventional clinical, radiological and/or endoscopic criteria, which was categorized as being acutely active (i.e. active clinical symptoms, and/or Crohn's disease activity index (CDAI) > 150 (Best 1976), and/or Pediatric Crohn's Disease Activity Index (PCDAI) > 15 (Hyams 1991), and/or a validated severity index indicating active disease (e.g. Harvey-Bradshaw Index (Harvey 1980), Van Hees Index (Van Hees 1980))).

Types of interventions

Trials were included if the primary intervention was traditional, systemically-active corticosteroid medication in any form (oral or parenteral). Topically-released corticosteroids were not considered for this review (e.g. enteric-coated budesonide, skin creams/ointments, inhaled fluticasone, enema therapy, etc.). Trials were only assessed if control groups were treated with placebo, 5-ASA preparations or sulfasalazine. Studies were not included if control groups were given other treatments (particularly budesonide, enteral nutrition and anti-tumour necrosis alpha therapy) because the comparison of these treatments to systemic corticosteroids have been the subject of previous meta-analysis published by the Cochrane

Library (Akobeng 2004; Otley 2005; Zachos 2007). Co-interventions were allowed only if they were balanced between the study groups, including but not restricted to immunomodulators, biologic therapy, and dietary therapy.

Types of outcome measures

The primary outcome measure was the number of patients achieving remission as defined by an absence of clinical symptoms (determined by the investigator), a CDAI < 150 or a PCDAI < 15 at weeks 4 to 6 (early), weeks 10 to 12 (middle), and weeks 15 or later (late) following initiation of therapy. Secondary outcomes included clinical response (as defined by the study authors), change in mean CDAI, presence of adverse events, and withdrawal rate of participants among the intervention and control groups (for toxicity and adverse events).

Search methods for identification of studies

See: Cochrane Inflammatory Bowel Disease and Function Bowel Disorders (IBD/FBD) Group methods used in reviews.

Electronic databases

An on-line database literature search was performed for human studies, without language restrictions, using the following databases: MEDLINE (NLM, National Library of Medicine, Bethesda; 1950 to January 2008), and EMBASE (Elsevier, NY; 1980 to January 2008) on OVID, as well as the Cochrane Central Register of Controlled Trials (The Cochrane Collaboration, UK; 2008, issue 1) and the Cochrane IBD/FBD Review Group Specialized Register (The Cochrane Collaboration, UK; January 31 2008). Ongoing trials were assessed using ClinicalTrials.gov (NLM, National Library of Medicine, Bethesda, February 7 2008). Proceedings from major gastrointestinal meetings (American Gastroenterology Association, British Society of Gastroenterology and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) were also manually searched from 2002 to 2007 in order to identify recent unpublished studies.

Search terms

The following keywords were used, including both text word [tw] and Medical Subject Heading (MeSH) terms (using the subheadings described) where appropriate and revised according to the database used:

1. inflammatory bowel diseases/ [MeSH] OR crohn disease/ [MeSH] OR (crohn$ OR (inflammatory ADJ2 bowel ADJ2 disease$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [tw]
2. glucocorticoids/ad, tu [MeSH] OR dexamethasone/ad, tu [MeSH] OR dexamethasone isonicotinate/ad, tu [MeSH] OR fluprednisolone/ad, tu [MeSH] OR methylprednisolone/ad, tu [MeSH] OR methylprednisolone hemisuccinate/ad, tu [MeSH] OR prednisolone/ad, tu [MeSH] OR prednisone/ad, tu [MeSH] OR hydrocortisone/ad, tu [MeSH] OR cortisone/ad, tu [MeSH] OR methylprednisole (nm) [MeSH] OR METHYLPREDNISOLONE HEMISUCCINATE/ [MeSH] OR PREDNISOLONE, THERAPEUTIC/ [MeSH] OR PREDNISONE, THERAPEUTIC/ [MeSH] OR cortisone, therapeutic/ [MeSH]
3. 1 AND 2
4. exp Placebos/ [MeSH] OR (placebo$ OR sham$ OR dummy$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] [tw]
5. exp MESALAMINE/ [MeSH] OR ("5-aminosalicylic$" OR "5-aminosalicylate$" OR "5-ASA" OR 5aminosalicylic$ OR 5aminosalicylate$ OR 5ASA OR pentasa OR mesalamine OR asacol).mp. [tw]
6. Sulfasalazine/ [MeSH] OR (sulfasalazine$ OR salazopyrin$ OR salazosulfapyridine$ OR asulfidine$ OR azulfadine$ OR azulfidine$).mp. [tw]
7. OR/4-6
8. 3 AND 7
9. limit 3 to randomized controlled trial
10. 9 NOT 8
11. from 10 keep 37, 45-46, 52
12. (random$ OR RCT OR RCTs OR ((singl$ OR doubl$ OR tripl$ OR trebl$) ADJ25 (mask$ OR blind$))).ti,ab. [tw]
13. 3 AND 12
14. 13 NOT (8 OR 9)
15. 8 OR 11

Other sources

Additional citations were identified by manually searching the reference lists of articles retrieved from the computerized databases and relevant review articles. Unpublished studies were sought by contacting experts in the field. The authors of published abstracts were contacted to obtain missing data.

Data collection and analysis

Selection of studies

Abstracts of all articles meeting the above search strategy were screened for eligibility. Full text studies were retrieved if they were potentially eligible for inclusion or if they were relevant review articles, for manual reference search. The retrieved full text articles were then independently reviewed by EIB and CHS for eligibility.

Data extraction and management

Two authors (EIB and CHS) independently completed a data extraction form for each eligible study. The following data was retrieved:

1. General information: title, journal, year, published/unpublished.
2. Study information: design (e.g. who was blinded), years of enrolment, crossover or not, methods used to ensure adequacy of randomization, concealment of allocation and blinding, power calculation (a priori and post hoc).

3. Intervention: formulation and dose of corticosteroid, conversion to prednisone-equivalents, type of comparison group, co-intervention.
4. Eligibility: inclusion/exclusion criteria, total number screened and randomized.
5. Baseline characteristics (in each group): age, sex, race, disease severity (and how evaluated), concurrent medications used, disease location, prior surgery, time since last surgery, CDAI/PCDAI, length of symptoms prior to randomization.
6. Follow-up: length of follow-up, assessment of compliance, withdrawals and loss to follow-up.
7. Outcome: cumulative remission and response rates in each group at weeks 2, 4, 6, 8, 10, 12, 15, 16, 17, and 18 following initiation of treatment or placebo, mean CDAI scores at each time point, and adverse event details.

Assessment of methodological quality of included studies

To assess methodological quality a five point ordinal scale (Jadad 1996) was independently completed by EIB and CHS for all eligible articles. Articles with poor quality (score of 0 to 2) were to be considered for subgroup analysis of low-quality studies. Since reliability of the Jadad score is not high (Clark 1999; Juni 2001), the final score was used only as a general guideline and decision on eligibility was accomplished by the mutual agreement of the authors based on the adequacy of concealment, blinding of intervention and outcome, and completeness of follow-up (Higgins 2005; Juni 2001). Studies were classified as "low risk of bias" (i.e. all above criteria met), "moderate risk of bias" (i.e. one or more criteria partly met) and "high risk of bias" (i.e. one or more criteria not met). When insufficient information was provided to determine the methodological quality, study authors were contacted to provide further details on the above criteria.

STATISTICAL ANALYSIS

Data were analyzed using Review Manager (RevMan 4.2.10, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2006). Categorical data (as presence or absence of remission at the three time points following initiation of treatment or placebo) for each study were transformed into 2x2 tables. The latest follow-up time point for each study was used for each of the three primary outcomes: Early remission (weeks 4 to 6), middle remission (weeks 10 to 12) and late remission (week 15 or later). For example if a study followed patients for 5 weeks after initiation of therapy, its outcomes were pooled with all studies following patients for 4 to 6 weeks. The last reported follow-up time point for each study was combined in order to account for differing patient follow-up lengths among studies.

Measures of treatment effect

The proportion of patients in remission was calculated and reported as relative risk and 95% confidence interval (95% CI). The number needed to treat (NNT) and absolute risk reduction (ARR) were also calculated where appropriate. Analysis of studies using placebo or 5-ASA/sulfasalazine in the control arms was conducted separately. Secondary outcomes such as presence of adverse events were also reported as above.

Meta-analysis

A random or fixed effects model was used to incorporate studies depending on clinical and statistical heterogeneity. Weighting of the studies was performed using the Mantel-Haenszel method (for fixed effects models) or the DerSimonian-Laird method (for random effects models).

Subgroup analysis and assessment for heterogeneity

Studies were independently reviewed for any clinical and methodological heterogeneity and possible reasons for heterogeneity were explored. The decision of whether to pool studies was aided by calculating the I^2 measure, interpreted as low heterogeneity (25%), moderate heterogeneity (50%) and high heterogeneity (75%) (Higgins 2003). Cochran's Chi-Square test for homogeneity (Q test) was performed with $P < 0.1$ being considered to be statistically significant due to its low sensitivity. The following a priori subgroup analyses were attempted, governed by the number of identified studies: corticosteroid dose (in prednisone equivalents), method of administration (intravenous versus oral), pediatric versus adult patients, different formulations of corticosteroids (e.g. prednisone, prednisolone, methylprednisolone, hydrocortisone, etc.) or 5-ASA (sulfasalazine, mesalamine, mesalazine, etc.), and disease location per the Montreal classification (Silverberg 2005). Studies with balanced co-interventions were also to be analyzed separately from studies without co-interventions, however the only study with balanced co-interventions (Rijk 1991) was not included due to lack of information on primary and secondary outcomes and failure to contact study authors after multiple attempts. Subgroups were chosen based on the possibility that differing doses, formulations and disease location may impact on treatment success. This is particularly true of certain 5-ASAs which have been suggested to be more successful at treating colonic disease given their predicted controlled-release characteristics.

Sensitivity analysis

In order to assess the robustness of the eligibility criteria, a sensitivity analysis was planned to exclude poor quality studies, studies published in an abstract form, studies not reporting methods to assess compliance and small studies (< 50 patients). No studies met these criteria. Too few studies were included to assess for publication bias using a funnel plot.

RESULTS

Description of studies

- See tables of included and excluded studies.

A total of six studies met inclusion criteria for meta-analysis (NCCDS; ECCDS; Scholmerich 1990; Martin 1990; Gross 1995; Prantera 1999). There were no disagreements between reviewers

(EIB and CHS) on study inclusion or study quality. Included studies can be distinguished by the comparison group. Two studies examined the efficacy of corticosteroids compared with placebo (while having a third treatment arm of subjects treated with sulfasalazine; NCCDS, ECCDS), while six studies compared corticosteroids to 5-ASA therapy (NCCDS; ECCDS; Scholmerich 1990; Martin 1990; Gross 1995; Prantera 1999). The included studies used different formulations and doses of corticosteroids and 5-ASA. Corticosteroid doses are expressed in the text, tables and figures as maximum dose in prednisone equivalents (the maximum amount of steroids received in one day) and cumulative dose over the first four weeks of study enrollment in prednisone equivalents. 5-ASA doses are expressed in daily 5-ASA ingested, with 500 mg of sulfasalazine being equivalent to 200 mg of 5-ASA (Sandborn 2003).

STUDIES COMPARING TRADITIONAL CORTICOSTEROIDS WITH PLACEBO

NCCDS 1979

The National Cooperative Crohn's Disease Study (NCCDS) was a multicentre, randomized, double-blind, placebo-controlled American study published in three parts (Summers 1979; Singleton 1979a; Winship 1979). Stratified randomization was based on: 1) patients having received steroids < 2 weeks prior to entry, 2) patients with isolated colonic disease versus all others, and 3) patients with CDAI > 150 versus patients with CDAI < 150. For those with active disease (CDAI 150 to 450), randomization assigned subjects to one of four arms: 1) Oral prednisone treatment at a dose of 0.50 to 0.75 mg/kg depending on severity of disease (based on CDAI) and toxicity (n = 85), 2) Sulfasalazine 1 g/15 kg of body weight to a maximum of 5 g/day (n = 74), 3) Azathioprine (not included in this meta-analysis, n = 59) and 4) Placebos alone (n = 77). All placebo tablets looked like the corresponding active tablets. The maximum daily dose of prednisone received was 60 mg/day, and the cumulative steroid dose over 4 weeks was 1680 mg of prednisone. The 5-ASA equivalent dose of 5 g/day of sulfasalazine is 2 g/day of 5-ASA ("Part I, Phase 1" of the study comprised of assessment of the medications for efficacy at inducing remission. Methods of the study were reported in Winship 1979, while Summers 1979 reported the results and Singleton 1979a reported adverse events. Remission was defined as a CDAI score of < 150. The primary outcome was proportion of patients in remission at week 17 after initiation of treatment and results are detailed in tabular form (Summers 1979, Table 7, "Outcome 6"). Remission at other time periods are described using life-table analysis with Kaplan-Meier curve (Summers 1979, Figure 4) however these time points could not be included in this meta-analysis due to the unavailability of raw numbers of patients entering remission. Mean CDAI change (week-by-week) are detailed in graphic form (Summers 1979, Figure 6).

ECCDS 1984

The European Cooperative Crohn's Disease Study (ECCDS) was similarly designed and conducted in multiple European countries (Malchow 1984). This study also included arms of patients with active disease (defined as CDAI > 150) and inactive disease (CDAI < 150). This meta-analysis only examined the former arm. Patients with active disease were randomized to one of four arms: 1) Oral 6-methylprednisolone at a dose of 48 mg/day for one week and then reduced to 32 mg, 24 mg, 20 mg, 16 mg and 12 mg on a weekly basis (n = 47), 2) Sulfasalazine 3 g/day (n = 54), 3) Combination therapy (steroids plus sulfasalazine, not included in this meta-analysis), or 4) Corresponding placebos (n = 58). Patients were followed for 18 weeks and proportion to enter remission was assessed after treatment. It is noteworthy that patients in the methylprednisolone groups were reassessed at the 3rd and 6th weeks following initiation of treatment. If adequate response was not achieved, the dose of steroids was increased again to 48 mg/day and the cycle was recommenced. This was repeated up to one more time, making three cycles of treatment possible. As such, it was difficult to calculate the cumulative dose of steroids received by these patients. Assuming no increase in the dose, patients received a maximum of 60 mg/day in prednisone-equivalents, and cumulative dose over four weeks was 945 mg of prednisone-equivalents. Sulfasalazine was administered at a dose equivalent to 1.2 g/day of 5-ASA. Remission was defined as a drop of CDAI to < 150 with a minimum decrease of 60 points after a maximum of 3 cycles of treatment. Although response to treatment was not clearly defined, this study detailed "lack of response", defined as withdrawal from study due to increase in CDAI during treatment or a slight increase in CDAI after two treatment cycles or documented worsened disease on interim x-ray. For the purposes of this review, we defined "response" as those patients who did not experience a "lack of response". The change in CDAI score is detailed (Malchow 1984, Figure 8A) for patients with active disease at study entry. Although the total number of adverse events was reported for each group, the proportion of patients experiencing at least one adverse event was not reported.

STUDIES COMPARING TRADITIONAL CORTICOSTEROIDS WITH 5-ASA

In addition to the above studies (which compared corticosteroids to placebo and sulfasalazine), four publications assessed the efficacy of corticosteroids compared with 5-ASA.

Scholmerich 1990

This was a randomized, controlled, double-blind, multicentre study conducted in Germany and Austria to assess the efficacy of mesalazine (Claversal®, Dr. Falk Pharma GmbH, Germany) compared with 6-methylprednisolone. Patients with active disease (CDAI 150 to 350 or van Hees Index > 200 and CDAI < 350) were randomized to either: 1) Oral 6-methylprednisolone at a dose of 48 mg/day for one week and then weaned to 32 mg, 24 mg, 20 mg, 16 mg, 12 mg and 8 mg weekly for a total course of 24 weeks (n = 32), or 2) Mesalazine 2 g/day for 24 weeks (n = 30). Maximum steroid dose was 60 mg/day of prednisone-equivalents and cumulative dose was 1085 mg of prednisone-equivalents over the first 4 weeks of study. The primary outcome was insufficient

efficacy as defined by fever > 39 degrees Celsius over six consecutive days, increase in CDAI to > 350, increase in CDAI of greater than 50 points since last visit, decrease of CDAI of less than 60 points and of van Hees Index of less than 30 points at week 4, or CDAI > 150 and van Hees Index > 200 at week 12. Upon review of the protocol with the corresponding author, we concluded that continued active disease (i.e. lack of remission) can be inferred from the definition of "insufficient efficacy" and this study was therefore included for analysis. Response to therapy (without remission) was not assessed by this study. This study detailed change in CDAI score between study entry and end of follow-up period is noted (Scholmerich 1990, Table 4). This group of investigators proceeded to compare 6-methylprednisolone to a higher dose of 5-ASA in a subsequent study (Gross 1995).

Martin 1990

Conducted in eight centres in Canada, this study was a randomized, controlled trial comparing Eudragit-L-100 coated mesalamine tablets (Salofalk) to oral prednisone. Patients with active disease (CDAI 200 to 450) were randomized to either: 1) Oral prednisone 40 mg/day for two weeks followed by a 4 mg/day weekly reduction for a total of 12 weeks (n = 28), or 2) Mesalamine 1 gram, three times per day for 12 weeks (n = 22). Maximum steroid dose was 40 mg/day of prednisone and cumulative dose was 1036 mg of prednisone over the first four weeks of study. Remission was defined as CDAI < 150 points. Patients were allowed to continue taking a maximum of 10 mg of prednisone throughout the study as they had been prescribed prior to enrollment. Patients were assessed every two weeks for clinical deterioration, defined as increase or absence of reduction of CDAI score, or any serious adverse events which prompted physician or patient to terminate the study. Response to therapy was defined as a "reduction in CDAI" score or remission. Change in CDAI score is detailed for Weeks 6 and 12 of treatment in graphic format (Martin 1990, Figure 1).

Gross 1995

As previously discussed, this study was performed by the same group who conducted a previous study (Scholmerich 1990) but assessed a higher dose of 5-ASA compared with 6-methylprednisolone. Patients with active disease (CDAI 150 to 350) were included if, at enrolment, they were taking < 10 mg/day of prednisone, < 2 g/day of 5-ASA and < 4 g/day of sulfasalazine. Patients were randomized to either: 1) Oral 6-methylprednisolone at a dose of 48 mg/day for one week and then weaned to 32 mg, 24 mg, 20 mg, 16 mg, 12 mg and 8 mg weekly for a total course of 8 weeks (n = 16), or 2) Mesalamine (Salofalk) 1.5 g, three times per day (4.5 g/day) for 8 weeks (n = 15). Maximum steroid dose was 60 mg/day of prednisone-equivalents and cumulative dose was 1085 mg of prednisone-equivalents over the first 4 weeks of study. For inclusion in intention to treat analysis, patients had to be treated for at least 7 days and CDAI calculated at week 8 or time of withdrawal. Remission was defined as CDAI < 150 and a decrease in CDAI of 60 or more points. This study was not sufficiently powered to detect the effect of medications based on disease phenotype. This study was powered to include 60 patients (30 per group), but was terminated early due to slow recruitment and expiration of the study drugs.

Prantera 1999

Conducted in 14 centres in Italy, this study was a double-blind, double-dummy, three-armed trial comparing 6-methylprednisolone to mesalamine (Asacol®, Giuliani S.P.A., Milan, Italy) in two different formulations. Patients with active disease (defined as CDAI 180 to 350) were eligible if their disease was limited to the distal ileum or distal ileum plus cecum. Computerized randomization in balanced blocks was done centrally for each centre, and patients were randomized to: 1) Oral 6-methylprednisolone 40 mg/day in three divided doses for two weeks and then tapered by 4 mg/day every week for 12 weeks (n = 31), or 2) Mesalamine tablets 4 g/day in three divided doses for 12 weeks (n = 35), or 3) Asacol (mesalamine) microgranular, a gelatin capsule containing 400 mg of mesalamine in microgranules coated with Eudragit S for optimal release in the distal ileum, at a total dose of 4 g/day in three divided doses for 12 weeks (n = 28). Appropriate dummies were produced for each group. Maximum steroid dose was 50 mg/day of prednisone-equivalents and cumulative dose was 1295 mg of prednisone-equivalents over the first 4 weeks of study. Remission was defined as a CDAI score of < 150.

Risk of bias in included studies

Methodological quality was independently assessed by two authors (EIB and CHS) using the Jadad scale, with 100% agreement in score. None of the eligible articles were excluded based on poor quality. The Jadad score for each study is detailed in the table of included studies. Two studies (Prantera 1999; Summers 1979) achieved Jadad scores of 5/5. One study (Martin 1990) achieved a score of 3/5 due to lack of detail on the method used to generate the sequence of randomization and no mention of the method of blinding, despite the study being described as double-blind. All other studies achieved Jadad scores of 4/5, and lost one point due to lack of detail concerning the method used to generate the sequence of randomization. Only two studies (Summers 1979; Prantera 1999) adequately described allocation concealment. Two studies (Gross 1995; Prantera 1999) failed to enrol sufficient patients to achieve their projected power. It is noteworthy that the reporting of adverse drug reactions was very heterogeneous between studies. Some studies very clearly noted the proportion of patients experiencing at least one drug-related adverse event (Singleton 1979a; Scholmerich 1990; Gross 1995), while others were less clear (Martin 1990; Prantera 1999). One study only reported on study withdrawals due to adverse events (Malchow 1984). Additionally, some studies reported adverse events as assessed by study physicians (Singleton 1979a; Scholmerich 1990), while others detailed events reported by patients (Gross 1995). This variety of methods used to report adverse events may have resulted in the

high degree of statistical heterogeneity found when pooling this data.

Effects of interventions

INDUCTION OF REMISSION: CORTICOSTEROIDS VERSUS PLACEBO

NCCDS 1979

The primary outcome in the NCCDS study was the proportion of patients in remission at week 17 after initiation of treatment. The results were reported in tabular form (Summers 1979, Table 7, "Outcome 6"). Remission at other time periods was described using life-table analysis with Kaplan-Meier curve (Summers 1979, Figure 4), however these time points could not be included in this meta-analysis due to the unavailability of raw numbers of patients entering remission. Following 17 weeks of treatment, 40 of 85 (47%) patients randomized to prednisone had entered remission, while 20 of 77 (26%) patients randomized to placebo had entered remission. In the sulfasalazine group, 31 of 74 (41.9%) patients entered remission. Although location of disease was examined as a predictor of outcome (with sulfasalazine and prednisone being superior to placebo for patients with colonic disease, whether or not the small bowel was involved), this comparison was based on relatively small numbers, making comparison between sulfasalazine and corticosteroids in patients with colonic disease unreliable. Additionally, although the improvement in outcome rank in treatment groups is noted (Summers 1979, Table 10), the proportion of patients with colonic disease who entered remission ("Outcome 6") was not reported. Raw data for this subgroup were unavailable.

ECCDS 1984

Following 18 weeks of treatment, 39 of 47 (83%) patients randomized to steroids, 27 of 54 (50%) patients randomized to sulfasalazine and 22 of 58 (37.9%) randomized to placebo had entered remission. Based on life-table analysis, the authors concluded that sulfasalazine was not effective in patients with small bowel disease (Malchow 1984, Table 13). Subgroup analysis on location of disease could not be included in this meta-analysis because the proportion of patients entering remission based on disease location was not provided. Raw data for this subgroup were unavailable.

Pooled Analysis

Both studies in this category reported statistically significant benefit of using corticosteroids to induce late remission in active CD (Comparison 01, Outcome 01). Although the studies used differing corticosteroid treatment regimens, they achieved similar remission rates. The pooled relative risk was also statistically significantly in favour of using corticosteroids to induce remission (RR 1.99; 95% CI 1.51 to 2.64; P < 0.00001). The absolute risk reduction (ARR) was 30% (95% CI 20% to 41%) and the number needed to treat (NNT) was 3.33 (95% CI 2.4 to 5.0). Combining the studies did not result in statistically significant heterogeneity (P = 0.50; I^2 = 0%). Although the raw data were not available for meta-analysis, it was clear from life-table data presented in Summers 1979 that corticosteroids showed benefit over placebo within 1 week of initiation of therapy. This benefit appeared to plateau at weeks 8 to 10 when approximately 70 to 80% of at-risk patients enter remission. A strong placebo effect was noted by Summers 1979, as after week 10 approximately 40% of at-risk patients continued to enter remission while on placebo.

INDUCTION OF REMISSION: CORTICOSTEROIDS VERSUS 5-ASA

NCCDS 1979 & ECCDS 1984

See above for comparison between the three treatment groups (placebo, corticosteroids and sulfasalazine).

Scholmerich 1990

Following 24 weeks of treatment, 21 of 32 (65.6%) patients in the steroid group entered remission compared to eight of 30 (26.7%) patients in the 5-ASA group. The study authors postulated that the lack of efficacy of the 5-ASA formulation was due to lack of release in the small bowel. No information was provided on the proportion of patients with disease confined to the colon only. This group of investigators proceeded to compare 6-methylprednisolone to a higher dose of 5-ASA in a subsequent study (Gross 1995).

Martin 1990

Following 12 weeks of treatment, 12 of 28 (42.8%) patients in the prednisone group had entered remission, compared to nine of 22 (40.9%) patients in the mesalamine group. No information was provided on remission rates based on disease phenotype. The study authors concluded that Salofalk provided no significant benefit for induction of remission compared with 'standard' therapy with prednisone.

Gross 1995

Remission was induced in nine of 16 (56.3%) patients in the 6-methylprednisolone group compared to six of 15 (40%) patients in the 5-ASA group at week 8. For the purposes of this meta-analysis, the remission rate at week 6 (early remission) was included for analysis, since the 8-week endpoint did not meet pre-specified criteria for middle remission (10 to 12 weeks). This study was not sufficiently powered to detect the effect of medications based on disease phenotype. This study was powered to include 60 patients (30 per group), but was terminated early due to slow recruitment and expiration of the study drugs.

Prantera 1999

At week 12 of treatment, remission was attained in 19 of 31 (61%) patients in the steroid group, compared to 21 of 35 (60%) patients in the 5-ASA tablet group and 22 of 28 (79%) patients in the 5-ASA granules group. For the purposes of this meta-analysis, the two 5-ASA groups were combined and compared with steroids. Interim remission rates are also reported by the authors, and are included in the early remission category (4 to 6 weeks) of this meta-analysis. The study was not powered to assess differences in disease location, however patients with more aggressive forms of CD (e.g. stricturing, fistulizing disease) were not included. Although more patients achieved remission in the 5-ASA microgranular group,

the differences between the three groups were not statistically significant. The power calculation provided in the text required enrollment of 73 patients per treatment group, however this was not achieved and the authors did not provide an explanation.

Pooled Analysis

After lengthy discussion amongst the reviewers (EIB and CHS) and content experts (AHS and AMG), it was decided that lack of raw data from the NCCDS (Summers 1979) and ECCDS (Malchow 1984) precluded pooling and meta-analysis of studies at the early and middle outcome time-points. The smaller studies showed no difference in efficacy between corticosteroids and 5-ASA for induction of remission at these earlier time-points (Gross 1995; Martin 1990; Prantera 1999). However, the NCCDS showed a clear benefit of corticosteroids compared to sulfasalazine by 2 to 4 weeks of treatment according to life table analysis (Summers 1979, Figure 4). Because the raw data from the NCCDS was not available for any time-point before the 17th week of study, pooling the other studies would lead to the biased conclusion that no difference existed in efficacy between 5-ASA and corticosteroids. Three studies (Summers 1979; Malchow 1984; Scholmerich 1990) compared the efficacy of corticosteroids and 5-ASA for induction of late remission (> 15 weeks following treatment initiation) (Comparison 02, Outcome 01). Pooled analysis revealed that corticosteroids were significantly better at inducing late remission than 5-ASA (RR 1.65; 95% CI 1.33 to 2.03; P < 0.00001). The ARR was 27% (95% CI 17% to 37%) and the NNT was 3.7 (95% CI 2.7 to 5.9). Pooling these studies did not result in significant heterogeneity (P = 0.33; I^2 = 10.2%). A sensitivity analysis was conducted by removing the single study that compared 5-ASA to corticosteroids (Scholmerich 1990) and leaving only studies comparing sulfasalazine and corticosteroids (Summers 1979; Malchow 1984). This resulted in no significant change in the RR from the original comparison (Comparison 02, Outcome 02).

CLINICAL RESPONSE TO TREATMENT AND CHANGE IN CDAI

NCCDS 1979

The NCCDS study did not report on clinical response. The mean CDAI scores at different time points were reported in graphic format (Summers 1979, Figure 6). Mean CDAI in the placebo group was reduced from 241.9 at baseline to 193 at Week 5 of treatment, 180 at Week 11 and then increased to 204 after 17 weeks of treatment (a decrease of 37.9 points from baseline). In the group receiving corticosteroids, mean CDAI decreased from 243.4 at baseline to 139 at Week 5, 120 at Week 11 and then remained at 120 at Week 17 (a decrease of 123.4 points from baseline). In the group receiving sulfasalazine, mean CDAI decreased from 256.2 at baseline to 165 at Week 5, 150 at Week 11, and 139 at Week 17 (a decrease of 117.2 points from baseline).

ECCDS 1984

As discussed above, "response" to treatment was defined as those patients who did not experience a "lack of response" for the purposes of this review. In the group receiving placebo, 31/58 patients (53.4%) responded to treatment. In the group receiving corticosteroids, 44/47 patients (93.6%) responded while in the group receiving sulfasalazine, 34/54 patients (62.9%) responded to treatment. Change in mean CDAI score was documented in graphic format only (Malchow 1984, Figure 8A). At baseline, patients in the placebo group had a mean CDAI of 200, those in the corticosteroids group had a mean CDAI of 245 and those in the sulfasalazine group had a mean CDAI of 260. Following approximately 1.5 months of treatment, all three groups had CDAI scores between 150 to 160. Following three months of treatment, the patients receiving prednisone had a mean CDAI of 85 (representing a decrease of 160 points from baseline), patients receiving sulfasalazine had a mean CDAI of 110 (a decrease of 150 points from baseline) and patients receiving placebo had a mean CDAI of 160 (a decrease of 40 points from baseline).

Scholmerich 1990

The clinical response rate was not reported in this study. Following 24 weeks of treatment, tabulated change in median CDAI scores (Scholmerich 1990, Table 4) showed that patients in the corticosteroids group decreased by 151 points, while those in the 5-ASA group decreased by 58 points (P < 0.001).

Martin 1990

Clinical response at 12 weeks was noted in 23/26 patients (88.5%) receiving corticosteroids compared with 16/19 patients (84.2%) receiving 5-ASA. Mean CDAI in the corticosteroid group decreased from 291 at baseline to 160 at Week 6 of treatment and 150 at Week 12 of treatment, representing a decrease of 141 points from baseline. Mean CDAI in the 5-ASA group decreased from 295 at baseline to 180 at Week 6 and 155 at Week 12, representing a decrease of 140 points from baseline.

Gross 1995

Clinical response was not reported in this study. In patients receiving corticosteroids, mean CDAI decreased from 236.2 at baseline to 102.2 after eight weeks of treatment (a decrease of 134 points). In patients receiving 5-ASA, mean CDAI decreased from 251.5 to 95.2 after eight weeks of treatment (a decrease of 156.3 points). There was no statistically significant difference between the change in CDAI scores between the two groups.

Prantera 1999

The clinical response rate was not reported in this study. In patients receiving corticosteroids, mean CDAI decreased by 154 points (95% CI 99 to 197) after 12 weeks of treatment. In patients receiving 5-ASA in tablet form, mean CDAI decreased by 113.5 points (95% CI 33 to 149) and in patients receiving 5-ASA in granular form, CDAI decreased by 123 points (95% CI 77 to 155). There was no statistically significant difference between the groups (P = 0.07). The authors concluded that steroids and the 5-ASA microgranular formulation resulted in a more rapid (although not statistically significant) decrease in CDAI.

Pooled Analysis

Clinical improvement or response to treatment was defined dif-

ferently (or not reported) in the above studies, making it inappropriate to combine these studies for pooled analysis. The response rates of the above studies are summarized in Comparison 01, Outcome 04 (for corticosteroids compared with placebo) and Comparison 02, Outcome 06 (for corticosteroids compared with 5-ASA). While most studies reported standard deviation of the mean CDAI at baseline, only one study reported standard error of the mean CDAI after treatment (Summers 1979). The remaining studies reported neither standard deviation nor standard error of the mean CDAI value following treatment, making combination of studies for the purpose of meta-analysis impossible.

ADVERSE EVENTS: CORTICOSTEROIDS VERSUS PLACEBO

NCCDS 1979

At least one adverse event was experienced by 27 patients in the prednisone group (31.8%) and 10 patients in the sulfasalazine group (14%), while only five patients in the placebo group experienced one adverse event (6.5%). Four patients from the prednisone group and 7 patients from the sulfasalazine group withdrew from the study due to adverse events or intolerance of medication, while no patients withdrew from the placebo group. A relatively high number of patients failed to complete the study. In the placebo group, 39 patients failed to continue treatment for 17 weeks (23 due to protocol violations, 13 due to disease worsening and three due to loss to follow-up). In the prednisone group, 30 patients failed to complete the study (18 due to protocol violations, four due to adverse events/intolerance, four due to disease worsening and four due to loss to follow-up). In the sulfasalazine group, 28 patients withdrew from the study (15 due to protocol violations, seven due to adverse events/intolerance, five due to worsening disease and one due to loss to follow-up).

ECCDS 1984

Although the total number of adverse events was reported for each group, this study did not report on the proportion of patients experiencing at least one adverse event. One patient in both the sulfasalazine and placebo groups, and two patients in the steroid group withdrew from the study due to adverse events or drug intolerance. Interestingly, all patients terminated treatment prior to the 18-week endpoint. In the placebo group, one withdrew due to medication-related adverse events/intolerance, eight due to requirement for surgery, five due to prolonged fever, 34 due to worsening/unchanged disease, three due to improved disease, one due to loss to follow-up and six due to non-compliance. In the methylprednisolone group, two withdrew due to adverse events/intolerance, two patients died during the study, one withdrew due to requirement for surgery, two due to fever, 11 due to worsening/unchanged disease, 15 due to improved disease, one due to loss to follow-up, one due to pregnancy and 12 due to non-compliance. In the sulfasalazine group, one patient died after the study, one patient withdrew due to adverse events/intolerance, six due to requirement for surgery, one due to fever, 34 due to worsening/unchanged disease , seven due to improved disease, one due to pregnancy and six due to non-compliance.

Pooled Analysis

The NCCDS study (Singleton 1979a) examined the proportion of patients experiencing one or more adverse events due to study medications (Comparison 01, Outcome 02). This study revealed a significantly higher likelihood of adverse events in patients who received corticosteroids compared to patients who received placebo (RR 4.89; 95% CI 1.98 to 12.07; P = 0.0006). The absolute risk increase (ARI) was 25% (95% CI 14% to 37%) and the number needed to harm (NNH) was 4 (95% CI 2.7 to 7.1) . Most of these adverse events were minor and did not result in study withdrawal. Study withdrawals due to adverse events or drug intolerance were described in two studies (Singleton 1979a; Malchow 1984). Neither study showed a statistically significant difference in study withdrawals between the corticosteroid and placebo groups (Comparison 01, Outcome 03). When pooled, there were more study withdrawals in patients who received corticosteroids compared to patients who received placebo. However, this difference was not statistically significant (RR 4.57; 95% CI 0.75 to 27.83; P = 0.10). Pooling these studies did not produce statistically significant heterogeneity (P = 0.52; I^2 = 0%).

ADVERSE EVENTS: CORTICOSTEROIDS VERSUS 5-ASA

NCCDS 1979 & ECCDS 1984

See above for comparison between the three treatment groups (placebo, corticosteroids and sulfasalazine).

Scholmerich 1990

Adverse events attributable to study medications were seen in 26% of patients treated with steroids compared to 11% of patients treated with 5-ASA. Two patients in each group withdrew due to adverse events or drug intolerance although details of the events and details of other study withdrawals were not provided.

Martin 1990

In the prednisone group, five patients did not complete the study (three due to adverse events/intolerance and two due to loss to follow-up), while five also failed to complete the study in the 5-ASA group (two due to adverse events/intolerance and three due to protocol violations). Reasons for withdrawal due to drug intolerance included headaches, intercostal herpes zoster infection and severe cushingoid symptoms in the prednisone group and headaches/vomiting and viral hepatitis in the 5-ASA group. A total of 16 minor adverse events were reported at 12 weeks in the prednisone group, compared with five minor adverse events in the 5-ASA group.

Gross 1995

One patient in each group withdrew due to drug intolerance and seven patients withdrew due to disease worsening (four from the steroid group and three from the 5-ASA group). Ten minor adverse events were noted in the steroid group and 11 minor adverse events were noted in the 5-ASA group.

Pooled Analysis

The number of patients experiencing at least one adverse event was reported in a number of studies comparing corticosteroids

to 5-ASA (Singleton 1979a; Martin 1990; Scholmerich 1990; Gross 1995; Prantera 1999). Most of these studies found more adverse events in patients taking corticosteroids, however two studies showed no statistically significant difference (Scholmerich 1990; Gross 1995) (Comparison 02, Outcome 03). When the studies were pooled, a trend towards more adverse events in the corticosteroid groups was seen (RR 3.13; 95% CI 0.99 to 9.90; P = 0.05). It is noteworthy that a high degree of statistical heterogeneity was produced by pooling these studies (P < 0.00001, I^2 = 87.8%). Sensitivity analysis was performed by grouping studies comparing corticosteroids only to low-doses (< 2 g/day) of 5-ASA (Singleton 1979a; Scholmerich 1990) (Comparison 02, Outcome 04). A significantly higher proportion of patients taking corticosteroids experienced at least one adverse event compared with patients taking low-dose 5-ASA (RR 2.38; 95% CI 1.34 to 4.25; P = 0.003). There was no significant heterogeneity in pooling these studies (P = 0.93; I^2 = 0%). When comparing groups receiving corticosteroids to high-dose (3 g/day or more) of 5-ASA, the statistical heterogeneity remained (P < 0.00001; I^2 = 94.2%) and no statistically significant difference between corticosteroid and 5-ASA groups is seen (RR 4.67; 95% CI 0.26 to 82.54; P = 0.29).

Studies were also assessed for withdrawal of patients due to adverse events. All six studies comparing corticosteroids to 5-ASA for induction of remission reported on study withdrawals (Singleton 1979a; Malchow 1984; Scholmerich 1990; Martin 1990; Gross 1995; Prantera 1999) (Comparison 02, Outcome 05). Meta-analysis revealed no significant difference in the numbers of patients withdrawing from studies when comparing patients receiving corticosteroids to those receiving 5-ASA (RR 1.18; 95% CI 0.61 to 2.29; P = 0.62). No significant heterogeneity resulted from pooling these studies (P = 0.26; I^2 = 23.8%).

DISCUSSION

Corticosteroids have been the mainstay of treatment for Crohn's disease for decades. The studies included in this review suggest that traditional corticosteroids are effective for induction of remission in patients with Crohn's disease. These studies also suggest that corticosteroids carry a significant risk of adverse events, particularly when compared with placebo and low-dose 5-ASA medications.

The efficacy of corticosteroids for induction of remission is confirmed by two large, randomized controlled studies comparing corticosteroids to placebo or sulfasalazine (Summers 1979; Malchow 1984). These studies used different corticosteroid treatment regimens. Summers 1979 used a continuing steady dose for the course of study while Malchow 1984 used a weaning course with the option to increase the dose if indicated. Both strategies provided similar efficacy for induction of remission at > 15 weeks and a similar risk of study withdrawal due to adverse events. Late follow-up also revealed a benefit of corticosteroids over 5-ASA medications for induction of remission, which was confirmed by a later study (Scholmerich 1990). All three studies used different formulations or doses of 5-ASA. Summers 1979 used sulfasalazine at the equivalent of 2 g/day of 5-ASA. Malchow 1984 used sulfasalazine at the equivalent of 1.2 g/day of 5-ASA. Scholmerich 1990 used mesalazine at a dose of 2 g/day of 5-ASA. Studies comparing corticosteroids and higher-dose 5-ASA (3 to 4.5 g/day) did not show a benefit for corticosteroids, although longer-term follow-up was not available (Martin 1990; Gross 1995; Prantera 1999). It is noteworthy that two of these studies ended prior to full patient enrollment based on their power calculations (Gross 1995; Prantera 1999), although sample size calculation was based on showing the benefit of 5-ASA over corticosteroids. Additionally, the NCCDS showed the clear benefit of corticosteroids over sulfasalazine at almost all early time-points (Summers 1979), but could not be included in pooled analysis due to the unavailability of raw data. In fact, sulfasalazine appeared no better than placebo in early treatment based on the life-table provided. As such, it was decided to avoid pooling of data comparing corticosteroids to 5-ASA at the early (4 to 6 weeks) and middle (10 to 12 weeks) outcome time-points. Both studies examining steroids and sulfasalazine versus placebo found that treatment was better than placebo at reducing CDAI at most time-points (Summers 1979; Malchow 1984). Only one study found that steroids caused a larger decrease in CDAI than low-dose 5-ASA (Scholmerich 1990), and this study followed patients for 24 weeks. The remaining studies were unable to show a difference in the decrease in mean CDAI in patients treated with steroids compared with 5-ASA. A number of factors may explain this finding. The studies that followed patients for shorter time periods were also small and may have been underpowered to detect a difference between interventions. The NCCDS (Summers 1979) showed a clear benefit for corticosteroids over 5-ASA for induction of remission from very early in the treatment course. Another explanation may be that corticosteroids are of equal value to high-dose 5-ASA for induction of remission in the short-term. The NCCDS utilized the equivalent of 2 g/day of 5-ASA, which is a much lower dose compared to that used in the studies with shorter study duration. This hypothesis requires proof in the form of a study using non-inferiority design, a strategy not employed by any of the studies in this review. A third explanation for the efficacy shown in some studies by 5-ASA formulations (when compared to corticosteroids) is that 5-ASA medications may be more advantageous in patients with primarily colonic disease. Although the phenotype of patients in the studies was sometimes documented, the small number of subjects with isolated colonic disease precluded analysis of this subgroup. It is noteworthy that in the largest studies (Summers 1979; Malchow 1984), sulfasalazine was superior to placebo in patients with colonic involvement, whether or not the small bowel was involved. The NCCDS concluded that prednisone was not effective against disease confined to the colon, although the authors warned that this finding was based on very few patients (Summers 1979). The ECCDS found that

sulfasalazine was not effective when the small bowel was involved and compared to placebo, both sulfasalazine and corticosteroids were effective when the colon was involved. Corticosteroids were most effective in patients with small bowel disease and combination therapy (sulfasalazine and 6-methylprednisolone) was most effective in patients with colonic disease. However, steroids and sulfasalazine were not compared head-to-head (Malchow 1984). Finally, it is noteworthy that in most studies, weaning of corticosteroids was initiated after 1 to 2 weeks of treatment, with no rise in dose as clinically indicated (with the exception of the ECCDS and NCCDS). This may have placed the corticosteroid groups at a disadvantage to the 5-ASA groups (who were treated at full-dose for the study course). None of the included studies administered parenteral corticosteroids for induction of remission, precluding a subgroup analysis based on route of corticosteroid delivery in this review. In summary, meta-analysis suggests that traditional corticosteroids are more effective than placebo and 5-ASA at inducing late remission in CD, but shorter term treatment benefits are unclear. Further well-powered and well-designed studies are required to assess the benefit of steroids in the short-term (compared with 5-ASA), as well as to assess the role of phenotype, disease location and method of delivery in predicting likelihood of remission.

This review focused on the efficacy of corticosteroids compared with placebo and 5-ASA. Other strategies are effective for inducing remission in Crohn's disease. Conventional corticosteroids have been found to be more effective for induction of remission than budesonide and enteral nutrition in active Crohn's (Otley 2005; Zachos 2007), although budesonide may be equivalent to systemic corticosteroids for ileal, cecal and ascending colon inflammation (Otley 2005). These reviews have demonstrated that both budesonide and enteral nutrition result in fewer adverse events than systemic corticosteroids. Additionally, azathioprine (Sandborn 2000), methotrexate (Alfadhli 2005), and biologic therapies (Akobeng 2004; MacDonald 2007) have all been found effective in active Crohn's, although direct comparisons to systemic corticosteroids are not available. The effectiveness of 5-ASA in active Crohn's has been controversial, as previously discussed. A recent meta-analysis of controlled clinical trials which included unpublished studies from the pharmaceutical industry has shown the limited efficacy of 5-ASA compared with placebo (Hanauer 2004). The continued debate potentially stems from differing study designs, the varying efficacy of different formulations and the possibility of better efficacy in colonic inflammation (Hanauer 2005; Kamm 2005; Stange 2005).

The risk of adverse events in patients using corticosteroids is less clear. Only one study (Singleton 1979a) examined the proportion of patients with at least one adverse event taking corticosteroids compared with placebo. This study showed a higher likelihood of adverse events in patients taking steroids. The same study showed more adverse events in the steroid group compared with the 5-ASA group. This was consistent with the findings of other studies comparing steroids to low-dose 5-ASA (1.2 to 2 g/day) (Malchow 1984; Scholmerich 1990). There was no difference in adverse events experienced by patients receiving corticosteroids compared with patients receiving higher-dose 5-ASA (3 to 4.5 g/day). The high degree of statistical heterogeneity is likely partly explained by the variation in definition of drug-related adverse event. In most cases, the study physician described a drug-related adverse event, but in some, the patient was given this responsibility. Some studies described patients with adverse events and did not clarify whether the events were drug-related. Additionally, most studies did not distinguish minor from serious adverse drug reactions. As a result of this variability in definition, some studies had > 50% of patients with at least one adverse event (Martin 1990; Gross 1995), while other studies described < 35% of patients with steroid-related effects (Singleton 1979a; Scholmerich 1990). Withdrawal from study due to drug intolerance or adverse events can be considered a proxy for serious drug-related adverse events. Patients receiving steroids showed no statistically significantly increased rate of study withdrawal compared with patients receiving 5-ASA or placebo. The assessment of the long-term effects of continuous or repeated corticosteroid administration is beyond the scope of this review, but should not be ignored by clinicians. In summary, although steroids may increase the risk of a patient experiencing one or more drug-related adverse event, they do not seem to increase the risk of study withdrawal due to serious adverse events.

AUTHORS' CONCLUSIONS

Implications for practice

The existing data suggest that corticosteroids are effective for induction of remission in Crohn's disease. Although further study is required to definitively assess whether steroids are more effective than 5-ASA in short-term therapy it is highly unlikely such trials will be performed. The analyses conducted in this review are limited by the design quality of the included studies and the unavailability of raw data. Treatment with steroids for active CD seems to be associated with a higher rate of adverse events compared with placebo and low-dose 5-ASA, but these events are not severe and did not result in increased rates of study withdrawal.

Implications for research

Although the benefit of corticosteroids over 5-ASA at inducing remission with short-term therapy is unclear, this may be due to a number of factors including unavailability of raw data, poor study design and poor study enrollment. Most clinicians treat active CD with full-dose steroids for 3 to 6 weeks followed by a gradual wean. The total course of therapy is often 3 to 4 months in duration and the benefits to patients receiving corticosteroids shown by this review at longer follow-up periods are clinically applicable. Should research be undertaken to compare corticosteroids to 5-ASA med-

ications in shorter term therapy, one might consider a non-inferiority trial design. Additional study is required to assess the role of method of corticosteroid delivery, phenotype and disease location in predicting the likelihood of inducing remission with corticosteroids, with particular attention to comparing steroids to 5-ASA therapy in patients with colonic disease.

ACKNOWLEDGEMENTS

This protocol was conducted as part of the University of Toronto graduate course "HAD5308 - Systematic Reviews & Meta-Analysis". We sincerely thank the course directors, Drs. Prakesh Shah and Joseph Beyene, for their teaching, guidance, comments and criticisms during the formulation of this protocol. We also thank Ms. Elizabeth Uleryk (Director, Hospital Library, The Hospital for Sick Children) for aiding in the search strategy used in this protocol.

Funding for the IBD/FBD Review Group (October 1, 2005 - September 30, 2010) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch; the Canadian Agency for Drugs and Technologies in Health (CADTH); and the CIHR Institutes of Health Services and Policy Research; Musculoskeletal Health and Arthritis; Gender and Health; Human Development, Child and Youth Health; Nutrition, Metabolism and Diabetes; and Infection and Immunity.

Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gross 1995

Methods	Randomized, controlled, double-blind, double-dummy multicentre study
Participants	Patients with CDAI 150-350 with onset of disease >3 months prior to study entry were eligible. Exclusion criteria: 1) Patients receiving glucocorticoids (>10 mg prednisolone/day), 5-ASA (>2 g/day), sulfasalazine (>4 g/day), azathioprine or metronidazole, 2) Intercurrent infection
Interventions	Group 1: 6-Methylprednisolone 48 mg/day for x1 wk then reduced to 32 mg, 24 mg, 20 mg, 16 mg, 12 mg and 8 mg weekly. Group 2: Mesalamine (Salofalk) 4.5 g/day for 8 weeks
Outcomes	"Remission" defined as CDAI<150 with a minimum 60 point decrease after 8 weeks of treatment
Notes	Study was terminated early (see text). Max Daily Dose (prednisone-equivalents) = 60 mg/d, Cumulative prednisone-equivalents over 4 weeks = 1085 mg, Maximum daily 5-ASA dose = 4.5 g/day. Jadad score 4/5 (no mention of the method used to generate the sequence of randomization)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Malchow 1984

Methods	Randomized, parallel group, double-blind, placebo-controlled trial. Study medication packaged centrally and labeled with code number. Placebo tablets looked like corresponding active tablet
Participants	Patients with CDAI >150 were eligible. Exclusion criteria included: 1) A diagnosis of CD >2 years before the study who did not require treatment, 2) Unwilling/unable to give informed consent, 3) Questionable ability to cooperate, 4) Investigator decision that study drugs pose risk to patients, 5) Symptoms of <3 months duration (to exclude acute ileitis), 6) Surgery impending (for toxic megacolon, gastrointestinal bleeding, peritonitis, etc.), 7) Age <18 years, 8) Other diseases requiring steroids or where steroids are contraindicated, 9) Decreased life-expectancy due to diseases other than CD, and 10) Pregnancy. Patients were stratified into those who had been previously treated for Crohn's and those who had not. For the purposes of this meta-analysis, all patients with active disease (CDAI>150) were included, regardless of whether or not they had been previously treated. Patient descriptions in Table 6 of the article are categorized by previously treatment but not by active vs. quiescent disease
Interventions	Group 1: 6-Methylprednisolone 48 mg/day x1 week then reduced to 32 mg, 24 mg, 20 mg, 16 mg and 12 mg on a weekly basis. Each cycle of treatment was evaluated at weeks 3 and 6. If remission was not induced at evaluation, the cycle would be repeated. The maximum number of cycles was three. Group 2: Sulfasalazine 3 g/day. Group 3: Combination therapy (steroid plus sulfasalazine) - not included in this meta-analysis. Group 4: Corresponding placebos Complete follow-up for patients with active disease was 18 weeks. If remission was induced, patients could enter a maintenance of remission study

Malchow 1984 (*Continued*)

Outcomes	"Remission" defined as a CDAI <150, "failure" was defined as failure to achieve CDAI <150 despite the interventions, death due to CD, surgery, new fistulas/abscesses, persistent fever, rise in CDAI of >100 points, any increase in CDAI during second cycle of treatment, insignificant (<60 point) decrease in CDAI despite 3 cycles of treatment or worsened condition based on radiology or endoscopy
Notes	Max Daily Dose (prednisone-equivalents) = 60 mg/d, Cumulative prednisone-equivalents over 4 weeks = 945 mg, Maximum daily 5-ASA dose = 1.2 g/day. Patients may have received more corticosteroid due to lack of remission at weeks 3 and 6. Jadad score 4/5 (no mention of the method used to generate the sequence of randomization)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Martin 1990

Methods	Randomized, controlled, double-blind, multicentre study.
Participants	Patients with CDAI 200-450 involving ileum (ileitis or ileocolitis) were eligible. Exclusion criteria: 1) Infectious enterocolitis, 2) Internal or external fistulizing disease, 3) Esophageal, gastric or jejunal disease, 4) Isolated colitis, 5) Prior bowel resection, 6) Hepatic, renal, cardiovascular or respiratory disease, 7) Treatment for active Crohn's within the past month (maximum prednisone dose of 10 mg was permitted)
Interventions	Group 1: Prednisone 40 mg/day x2 weeks , followed by a weekly wean of 4 mg/day for a total 12 week course. Group 2: Four 250 mg Eudragit-L-100 coated 5-ASA tablets (Salofalk) three times per day (3 g/day) for 12 weeks
Outcomes	"Remission" defined as a CDAI<150 with a minimum 60 point decrease after 8 weeks of treatment. "Failure" was considered by clinical deterioration, confirmed by an increase or absence of reduction of the CDAI score, or any serious side effect occurring during the trial period prompting termination of study enrollment
Notes	Max Daily Dose (prednisone-equivalents) = 40 mg/d, Cumulative prednisone-equivalents over 4 weeks = 1036 mg, Maximum daily 5-ASA dose = 3 g/day. Jadad score 3/5 (no mention of the method used to generate the sequence of randomization and no mention of the method of blinding, although the study is described as double-blind)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Prantera 1999

Methods	Randomized, double-blind, double-dummy, multicentre trial with three parallel groups
Participants	Patients with CDAI 180-350 involving distal ileum (ileitis or ileocolitis) were eligible. Exclusion criteria: 1) Intestinal fistulizing disease and abdominal mass, 2) Active perianal disease, 3) Previous small bowel resection >100 cm, previous colectomy or proctocolectomy, 4) Pregnancy, 5) Any disease that does not permit steroid use
Interventions	Group 1: 6-Methylprednisolone 40 mg/day for two weeks and then reduced weekly by 4 mg/day for a 12 week course. Group 2: Mesalamine (Asacol) was administered in two preparations: a) Asacol tablets, and b) Asacol microgranular. For both formulations, 4 g/day were given for 7 weeks (divided three times per day) and then tapered to 3.2 g/day after 7 weeks and 2.4 g/day after 10 weeks. For the purposes of this meta-analysis, the two mesalamine preparations were pooled and compared with 6-Methylprednisolone
Outcomes	"Remission" defined as a CDAI<150 after 12 weeks of treatment
Notes	Insufficient patients enrolled to meet power (see text). Max Daily Dose (prednisone-equivalents) = 50 mg/d, Cumulative prednisone-equivalents over 4 weeks = 1295 mg, Maximum daily 5-ASA dose = 4 g/day. Jadad score 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Scholmerich 1990

Methods	Randomized, controlled, double-blind, multicentre study.
Participants	Patients with active Crohn's disease (CDAI 150-350 or Van Hess Index score >200 with CDAI<350) . Exclusion criteria: 1) Present flare of disease already treated with sulfasalazine, 5-ASA, steroids, immunosuppressive drugs or elemental diet, 2) Intercurrent infection, 3) Maintenance treatment until flare-up with at least 20 mg/day methylprednisolone, 1.5 g/day 5-ASA or 3 g/day sulfasalazine
Interventions	Group 1: 6-Methylprednisolone 48 mg/day x1 week and then reduced to 32, 24, 20, 16, 12 and 8 mg on a weekly basis, with 8 mg continuing for 18 weeks, for a total 24 week course. Group 2: Mesalamine (Claversal) 2 g/day for 24 weeks
Outcomes	Criteria for "insufficient efficacy" were: 1) fever >39 degrees Celcius over six consecutive days, 2) Increase in CDAI to >350, 3) Increase of CDAI of greater than 50 points since last visit, 4) Decrease of CDAI of less than 60 and of Van Hess Index of less than 30 at week 4, 5) CDAI>150 and Van Hess Index>200 at week 12. Upon review of the protocol with the corresponding author, we conclude that continued active disease (i.e. lack of remission) can be inferred from the definition for "insufficient efficacy" and we therefore included this study for analysis
Notes	Max Daily Dose (prednisone-equivalents) = 60 mg/d, Cumulative prednisone-equivalents over 4 weeks = 1085 mg, Maximum daily 5-ASA dose = 2 g/day. Jadad score 4/5 (no mention of the method used to generate the sequence of randomization)

Scholmerich 1990 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Singleton 1979a

Methods	National Cooperative Crohn's Disease Study (NCCDS) - Adverse Reactions to Study Drugs
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Summers 1979

Methods	National Cooperative Crohn's Disease Study (NCCDS) - Results of Drug Treatment. Complete methods are published in a separate article (Winship, 1979). Randomized, parallel group, double-blind, placebo-controlled trial. Stratified randomization based on: 1) Patients having received steroids <2 weeks ago vs. others, 2) Patients with isolated colonic disease vs. others, 3) Patients with CDAI>150 vs. patients with CDAI<150. Placebo tablets looked like corresponding active tablet. Assessment of medications for induction of remission was "Part I, Phase 1" of the study
Participants	Patients with CDAI 150-450 were eligible. Exclusion criteria included: 1) No previous history of small intestinal or colonic disease who at laparotomy had not chronic inflammatory changes of the bowel, 2) Patients with proctitis only, 3) Patients with immediate need for surgery or requiring transfusion more than 500 ml/week or intestinal obstruction, 4) Patients with tuberculosis or systemic fungal infection, 5) Children under 15 years old, 6) Patients with hypertension requiring more than thiazide treatment, 7) Patients with diabetes mellitus, 8) Patients with significant liver disease, renal disease, symptomatic osteoporosis or amyloidosis, 9) Pregnancy, 10) Unwilling/unable to provide informed consent, 11) Significant leukopenia or thrombocytopenia
Interventions	Group 1: Prednisone 0.5-0.75 mg/kg depending on severity of disease (based on CDAI) and toxicity. Group 2: Sulfasalazine 1 g/15kg of body weight (maximum 5 g/day). Group 3: Azathioprine (not included in this meta-analysis). Group 4: Corresponding placebos only. If remission was induced, patients could enter a maintenance of remission study. "Part I, Phase 1" was complete after 17 weeks of treatment

Summers 1979 (*Continued*)

Outcomes	"Remission" was defined as a CDAI <150. For "Part I, Phase 1", the principal response criterion was the CDAI at the end of 17 weeks. Patients were ranked on the basis of outcome, and "Outcome 6" (Table 7) being defined as CDAI<150 at the end of follow-up. Note remission rates at other time periods within 17 weeks are noted in Figure 4 in life-table format with Kaplan-Meier curve, but these intermediate time points could not be included in this meta-analysis due to unavailability of raw number of patients entering remission
Notes	Max Daily Dose (prednisone-equivalents) = 60 mg/d, Cumulative prednisone-equivalents over 4 weeks = 1680 mg, Maximum daily 5-ASA dose = 2 g/day. Patients may have received less corticosteroid or sulfasalazine based on lower body weight. Jadad score 5/5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Winship 1979

Methods	National Cooperative Crohn's Disease Study (NCCDS) - Study Design and Conduct of the Study. Complete methods are detailed in this publication
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bergman 1976	Examined prednisone and salazopyrin to maintain surgically-induced remission. Included patients in remission (not active). Control group received no treatment

(*Continued*)

Brignola 1994	Compared two different tapering regimens of methylprednisolone in active Crohn's disease. No placebo or 5-ASA control group
Chun 1998	Compared adrenocorticotrophic hormone (ACTH) to methylprednisolone in active Crohn's. No placebo or 5-ASA control group
Gaia 1979	Compared two different prednisolone regimens in active Crohn's disease. No placebo or 5-ASA control group
Jenss 1989	Preliminary results of an included trial (Scholmerich, 1990)
Jenss 1990	Preliminary results of an included trial (Scholmerich, 1990)
Landi 1992	Compared two different tapering regimens of prednisolone in active Crohn's disease. No placebo or 5-ASA control group. Includes patients already in remission. Primary outcome is maintenance of clinical and endoscopic remission
Maier 1990	Compared sulfasalazine/methylprednisolone in one group to mesalazine in the other group. Concomitant therapy was not balanced in both groups, therefore it was impossible to assess the efficacy of the corticosteroid treatment
Modigliani 1990	All patients enrolled received prednisolone. No placebo or 5-ASA control group. The objective of the study was to correlate clinical, biologic and endoscopic features during induction of remission
Modigliani 1996	Patients enrolled in steroid-induced remission. The objective of the study was to assess mesalamine in maintaining remission while withdrawing steroids
Rijk 1991	Compared two groups: 1) Sulfasalazine 6 g/day (or 4 g/day if side effects occur) + placebo vs. 2) Sulfasalazine 6 g/day + prednisone 30 mg/day. This study compared relative changes in the raw score of two activity indices and did not report remission rates. Limited or no information is available to examine side effects. Unsuccessful attempts were made to contact the study authors to obtain this information, and the study was therefore excluded
Schneider 1985	Compared three treatments: 1) Prednisone plus salazopyrin, 2) Prednisone plus salazopyrin and metronidazole, and 3) Metronidazole alone. The concomitant treatments were not balanced in all groups and it was therefore impossible to assess the efficacy of the corticosteroids therapy
Singleton 1979b	Both study groups received prednisone. One group received prednisone and placebo, the other group received prednisone and sulfasalazine. The objective of the study was not to assess efficacy of prednisone

DATA AND ANALYSES

Comparison 1. Corticosteroids vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission rate (Late, 15+ weeks)	2	267	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.51, 2.64]
2 Development of Any Adverse Event	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Withdrawal From Study Due To Adverse Event	2	267	Risk Ratio (M-H, Fixed, 95% CI)	4.57 [0.75, 27.83]
4 Response to Treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Corticosteroids vs. 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission Rate (Late, 15+ weeks) (Max Pred 60 mg/day + 5-ASA 1.2-2 g/day)	3	322	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.33, 2.03]
2 Remission Rate (Late, 15+ weeks) (Sensitivity Analysis - Sulfasalazine studies only)	2	260	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.23, 1.91]
3 Development of Any Adverse Event	5	396	Risk Ratio (M-H, Random, 95% CI)	3.13 [0.99, 9.90]
4 Development of Any Adverse Event (Sensitivity Analysis - Removed high-dose 5-ASA studies)	2	221	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.34, 4.25]
5 Withdrawal from Study Due to Adverse Event	6	478	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.61, 2.29]
6 Response to Treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

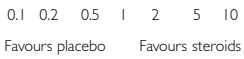
Analysis 1.1. Comparison 1 Corticosteroids vs. placebo, Outcome 1 Remission rate (Late, 15+ weeks).

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 1 Corticosteroids vs. placebo

Outcome: 1 Remission rate (Late, 15+ weeks)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Malchow 1984	39/47	22/58		48.4 %	2.19 [1.54, 3.12]
Summers 1979	40/85	20/77		51.6 %	1.81 [1.17, 2.81]
Total (95% CI)	**132**	**135**		**100.0 %**	**1.99 [1.51, 2.64]**
Total events: 79 (Corticosteroids), 42 (Placebo)					
Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 4.82 (P < 0.00001)					



Analysis 1.2. Comparison 1 Corticosteroids vs. placebo, Outcome 2 Development of Any Adverse Event.

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 1 Corticosteroids vs. placebo

Outcome: 2 Development of Any Adverse Event

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Summers 1979	27/85	5/77		4.89 [1.98, 12.07]

Analysis 1.3. Comparison 1 Corticosteroids vs. placebo, Outcome 3 Withdrawal From Study Due To Adverse Event.

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 1 Corticosteroids vs. placebo

Outcome: 3 Withdrawal From Study Due To Adverse Event

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Malchow 1984	2/47	1/58		63.1 %	2.47 [0.23, 26.39]
Singleton 1979a	4/85	0/77		36.9 %	8.16 [0.45, 149.19]
Total (95% CI)	**132**	**135**		**100.0 %**	**4.57 [0.75, 27.83]**

Total events: 6 (Corticosteroids), 1 (Placebo)

Heterogeneity: $Chi^2 = 0.41$, df = 1 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 1.65 (P = 0.099)

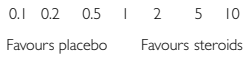
Analysis 1.4. Comparison 1 Corticosteroids vs. placebo, Outcome 4 Response to Treatment.

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 1 Corticosteroids vs. placebo

Outcome: 4 Response to Treatment

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Malchow 1984	44/47	31/58		1.75 [1.36, 2.25]



Analysis 2.1. Comparison 2 Corticosteroids vs. 5-ASA, Outcome 1 Remission Rate (Late, 15+ weeks) (Max Pred 60 mg/day + 5-ASA 1.2-2 g/day).

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 2 Corticosteroids vs. 5-ASA

Outcome: 1 Remission Rate (Late, 15+ weeks) (Max Pred 60 mg/day + 5-ASA 1.2-2 g/day)

Study or subgroup	Corticosteroids n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Malchow 1984	39/47	27/54		37.8 %	1.66 [1.23, 2.23]
Scholmerich 1990	21/32	8/30		12.4 %	2.46 [1.29, 4.69]
Summers 1979	51/85	31/74		49.8 %	1.43 [1.04, 1.97]
Total (95% CI)	**164**	**158**		**100.0 %**	**1.65 [1.33, 2.03]**
Total events: 111 (Corticosteroids), 66 (5-ASA)					
Heterogeneity: Chi^2 = 2.23, df = 2 (P = 0.33); I^2 =10%					
Test for overall effect: Z = 4.64 (P < 0.00001)					

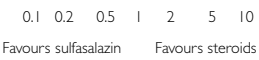
Analysis 2.2. Comparison 2 Corticosteroids vs. 5-ASA, Outcome 2 Remission Rate (Late, 15+ weeks) (Sensitivity Analysis - Sulfasalazine studies only).

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 2 Corticosteroids vs. 5-ASA

Outcome: 2 Remission Rate (Late, 15+ weeks) (Sensitivity Analysis - Sulfasalazine studies only)

Study or subgroup	Corticosteroids n/N	Sulfasalazine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Malchow 1984	39/47	27/54		43.1 %	1.66 [1.23, 2.23]
Summers 1979	51/85	31/74		56.9 %	1.43 [1.04, 1.97]
Total (95% CI)	**132**	**128**		**100.0 %**	**1.53 [1.23, 1.91]**
Total events: 90 (Corticosteroids), 58 (Sulfasalazine)					
Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 3.78 (P = 0.00016)					



Analysis 2.3. Comparison 2 Corticosteroids vs. 5-ASA, Outcome 3 Development of Any Adverse Event.

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 2 Corticosteroids vs. 5-ASA

Outcome: 3 Development of Any Adverse Event

Study or subgroup	Corticosteroids n/N	5-ASA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gross 1995	11/16	12/15		24.3 %	0.86 [0.57, 1.30]
Martin 1990	16/28	2/22		18.6 %	6.29 [1.61, 24.49]
Prantera 1999	12/31	1/63		14.3 %	24.39 [3.32, 179.15]
Scholmerich 1990	8/32	3/30		19.5 %	2.50 [0.73, 8.55]
Singleton 1979a	27/85	10/74		23.2 %	2.35 [1.22, 4.53]
Total (95% CI)	**192**	**204**		**100.0 %**	**3.13 [0.99, 9.90]**
Total events: 74 (Corticosteroids), 28 (5-ASA)					
Heterogeneity: Tau^2 = 1.38; Chi^2 = 32.66, df = 4 (P<0.00001); I^2 =88%					
Test for overall effect: Z = 1.94 (P = 0.052)					

Analysis 2.4. Comparison 2 Corticosteroids vs. 5-ASA, Outcome 4 Development of Any Adverse Event (Sensitivity Analysis - Removed high-dose 5-ASA studies).

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 2 Corticosteroids vs. 5-ASA

Outcome: 4 Development of Any Adverse Event (Sensitivity Analysis - Removed high-dose 5-ASA studies)

Study or subgroup	Corticosteroids n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Scholmerich 1990	8/32	3/30		22.5 %	2.50 [0.73, 8.55]
Singleton 1979a	27/85	10/74		77.5 %	2.35 [1.22, 4.53]
Total (95% CI)	**117**	**104**		**100.0 %**	**2.38 [1.34, 4.25]**
Total events: 35 (Corticosteroids), 13 (5-ASA)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 2.94 (P = 0.0032)					

Analysis 2.5. Comparison 2 Corticosteroids vs. 5-ASA, Outcome 5 Withdrawal from Study Due to Adverse Event.

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 2 Corticosteroids vs. 5-ASA

Outcome: 5 Withdrawal from Study Due to Adverse Event

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gross 1995	1/16	1/15		7.6 %	0.94 [0.06, 13.68]
Malchow 1984	1/58	1/52		7.8 %	0.90 [0.06, 13.97]
Martin 1990	3/28	2/22		16.5 %	1.18 [0.22, 6.45]
Prantera 1999	5/31	1/63		4.9 %	10.16 [1.24, 83.27]
Scholmerich 1990	2/32	2/30		15.2 %	0.94 [0.14, 6.24]
Singleton 1979a	4/85	5/46		47.9 %	0.43 [0.12, 1.53]
Total (95% CI)	**250**	**228**		**100.0 %**	**1.18 [0.61, 2.29]**

Total events: 16 (Corticosteroids), 12 (Placebo)

Heterogeneity: Chi^2 = 6.56, df = 5 (P = 0.26); I^2 =24%

Test for overall effect: Z = 0.49 (P = 0.62)

Analysis 2.6. Comparison 2 Corticosteroids vs. 5-ASA, Outcome 6 Response to Treatment.

Review: Traditional corticosteroids for induction of remission in Crohn's disease

Comparison: 2 Corticosteroids vs. 5-ASA

Outcome: 6 Response to Treatment

Study or subgroup	Corticosteroids n/N	5-ASA n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Malchow 1984	44/47	34/54		1.49 [1.20, 1.85]
Martin 1990	23/26	16/19		1.05 [0.83, 1.33]

WHAT'S NEW

Date	Event	Description
1 March 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 2, 2008

Date	Event	Description
15 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

EIB formulated the study question and wrote the manuscript.

CHS assisted with the search strategy and reviewed the manuscript.

AHS acted as content expert and reviewed the manuscript.

AMG formulated the study question, assisted with the study design and reviewed the manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- EIB, Clinician-Scientist Training Program, The Hospital for Sick Children, Toronto, Ontario, Canada.
- EIB/CHS/AHS, Department of Health Policy, Management & Evaluation, University of Toronto, Toronto, Ontario, Canada.
- AHS, Mount Sinai Hospital, Department of Gastroenterology, Toronto, Ontario, Canada.
- AMG, The Hospital for Sick Children, Toronto, Ontario, Canada.

External sources

- CHS, Richard Walter Gibbon Medical Research Fellowship, University of Western Australia, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Crohn Disease [*drug therapy]; Randomized Controlled Trials as Topic; Remission Induction

MeSH check words

Humans