Authors' objectives
To assess the effectiveness and safety of budesonide in comparison with corticosteroids, 5-aminosalicylic acid (5-ASA) or placebo, for inducing remission of active Crohn's disease and for maintaining remission.

Searching
MEDLINE and EMBASE were searched from 1980 to 2001 for articles in any language. The search terms used were 'budesonide', 'Crohn disease', 'therapy', 'clinical trial' and 'randomized (pt)'. In addition, reference lists and conference proceedings of the American Gastroenterological Association and the American College of Gastroenterology were handsearched. Researchers and drug companies were contacted for unpublished trials.

Study selection
Study designs of evaluations included in the review
Randomised trials with a parallel-group design were included.

Specific interventions included in the review
The specific interventions were budesonide, corticosteroids, 5-ASA products or placebo.

Participants included in the review
Adults with Crohn's disease were included.

Outcomes assessed in the review
The study selection criteria specified the evaluation of adverse events and the evaluation of induction or maintenance of remission, as defined by Crohn's Disease Activity Index (CDAI) scores of 150 or less. The actual primary study outcomes were: the proportion of patients in remission, as defined by CDAI scores of 150 or less; the proportion of patients with any adverse event; and the proportion of patients with corticosteroid-associated adverse events.

How were decisions on the relevance of primary studies made?
Two investigators independently reviewed the titles and abstracts of all citations identified by the literature search. Both investigators independently retrieved and reviewed the reports of potentially relevant studies and applied detailed selection criteria.

Assessment of study quality
The studies were assessed for adequacy of randomisation, allocation concealment, double-blinding, and completeness of follow-up, using a validated 5-point methodological quality tool (see Other Publications of Related Interest no.1). Two investigators independently assessed the methodology of each individual study included in the meta-analysis, using standardised forms. The original study protocols were requested when a full assessment of study methodology could not be completed from the published report.

Data extraction
Two investigators independently extracted the data using pre-tested, standardised forms. Any disagreements were resolved through consensus. When specific data concerning adverse events or patient outcomes were not available in the published reports, additional data were requested from the investigators. According to the authors, the extracted data concerned populations, interventions, study duration and outcomes; the data tables were missing from the report.

Methods of synthesis
How were the studies combined?
The methods of DerSimonian and Laird (see Other Publications of Related Interest no.2) were used to calculate the pooled effects estimates. The measure of association was the relative risk (RR), and the 95% confidence intervals (CIs) were calculated to assess the precision of the estimates. In addition, the number-needed-to-treat or number-needed-to-harm, and the absolute risk reduction or absolute benefit increase were calculated for each statistically-significant outcome.

How were differences between studies investigated?
The methods of DerSimonian and Laird (see Other Publications of Related Interest no.2) were used to assess heterogeneity between the trials and for each outcome using a random-effects model.

Sensitivity analyses of remission among patients with low (CDAI score: 200 to 300) or high (CDAI score greater than 300) disease activity were planned. Post hoc sensitivity analyses were conducted on the proportion of non-steroid dependent patients who maintained remission after medically- or surgically-induced remission of active Crohn's disease. Such analyses were also conducted on the proportion of steroid-dependent patients who maintained remission of quiescent Crohn's disease after randomisation to budesonide or 5-ASA or placebo. Sensitivity analyses were also conducted for studies that used a higher maintenance treatment of budesonide (i.e. 6 mg, 4 times daily) for maintenance of remission.

Results of the review
Sixteen randomised clinical trials involving 1,291 patients were accepted for the meta-analysis. Of these, 13 were published and 3 were ‘in press’.

Budesonide was more likely to induce remission than placebo (RR 1.82, 95% CI: 1.15, 2.88) or 5-ASA (RR 1.73, 95% CI: 1.26, 2.39), although only one trial compared budesonide with 5-ASA products. Although budesonide induced remission less frequently than conventional corticosteroids (RR 0.87, 95% CI: 0.76, 0.995), there was no significant difference between conventional corticosteroids and budesonide for inducing remission among patients with a low disease activity (initial CDAI: 200 to 300). Budesonide was significantly less likely to cause corticosteroid-associated adverse events than conventional corticosteroids (RR 0.65, 95% CI: 0.53, 0.80). No significant difference in total adverse events or corticosteroid-associated adverse events was demonstrated between budesonide and 5-ASA or placebo.

Authors’ conclusions
Budesonide is significantly more effective than placebo for inducing remission of active Crohn's disease. While budesonide is 13% less effective for the induction of remission in active Crohn's disease than conventional corticosteroids, it is less likely to cause corticosteroid-related adverse effects. Budesonide is ineffective in maintaining remission.

CRD commentary
The review asked clear questions, and the authors appear to have followed an explicit protocol in attempting to answer them. A comprehensive search strategy was used to locate published and unpublished studies. The study selection, validation and data extraction processes were performed in duplicate, and analytical strategies were predefined. The absence of the tabulated trial from the published report is unfortunate; it prevents an independent estimation of trial heterogeneity and replication of the reviewers’ analysis. The review was funded by an unrestricted educational grant from the manufacturer of budesonide (AstraZeneca, LP), thus raising the possibility of conflict of interest.

Implications of the review for practice and research
Practice: Budesonide has superior tolerability in comparison to corticosteroids, with no demonstrated difference in effectiveness among patients who present with low disease activity (CDAI: 200 to 300). Nevertheless, treatment selection resides at the level of the individual patient.
Research: Several questions need addressing. First, are patients with active Crohn's disease who received budesonide more likely to become dependent upon corticosteroids than patients who receive other forms of therapy? Second, what are the effects of long-term budesonide therapy on bone metabolism? Further randomised controlled trials comparing budesonide and 5-ASAs are needed to define the relative benefits and adverse effects of these treatments.

Funding
AstraZeneca, LP.

Bibliographic details

PubMedID
12182751

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents /therapeutic use; Anti-Inflammatory Agents, Non-Steroidal /therapeutic use; Budesonide /therapeutic use; Crohn Disease /drug therapy; Glucocorticoids /therapeutic use; Humans; Mesalamine /therapeutic use; Randomized Controlled Trials as Topic; Remission Induction

AccessionNumber
12002002002

Date bibliographic record published
30/06/2003

Date abstract record published
30/06/2003

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.