The role of inhaled corticosteroids and montelukast in children with mild-moderate asthma: results of a systematic review with meta-analysis

Castro-Rodriguez JA, Rodrigo GJ

CRD summary
This review concluded that inhaled corticosteroids led to less asthma exacerbations compared with montelukast for the prevention of asthma exacerbations in children with mild-to-moderate persistent asthma. Although there was uncertainty related to some aspects of the reporting of the review, the authors’ conclusions reflected the evidence presented and appear to be broadly reliable.

Authors’ objectives
To assess the efficacy of inhaled corticosteroids and montelukast for the prevention of asthma exacerbations in children and adolescents with mild-to-moderate persistent asthma.

Searching
MEDLINE (from 1966 to November 2009), EMBASE (from 1980 to November 2009), and Cochrane Central Register of Controlled Trials (CENTRAL, third quarter 2009) were searched, with no language restrictions. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared inhaled corticosteroids with montelukast or with inhaled corticosteroids plus montelukast in patients (aged less than 18 years) with a clinical diagnosis of asthma for at least six months before entry into the trial, were eligible for inclusion. The treatment had to last at least four weeks and the dose of inhaled corticosteroids had to be maintained throughout the intervention period. Trials published in abstract form were excluded.

The primary outcome was asthma exacerbations, defined as worsening symptoms requiring systemic corticosteroid use. Secondary outcomes included final pulmonary function (defined as forced expiratory volume in the first second - FEV₁), hospitalisation due to asthma exacerbations, adverse events, and adherence.

In included trials, the inhaled corticosteroids assessed were budesonide, beclomethasone, fluticasone propionate, and triamcinolone. The dose of inhaled corticosteroids was 200 to 300μg/day of beclomethasone or equivalent; the dose of montelukast was 5 to 10mg/day. No trials used additional anti-asthmatic drugs, other than rescue beta₂-agonists and oral corticosteroids. The mean age of included patients was 9.7 years, 63% were male (range 54 to 80%), and their baseline FEV₁ was 81% (range 64 to 98%). The trials included multicentre and crossover trials. Most of the included trials were funded by pharmaceutical companies (where reported).

Two reviewers independently applied the inclusion criteria; there were no disagreements.

Assessment of study quality
The quality of the included trials was assessed on randomization, double-blinding and withdrawal/dropout using the Jadad scale. The quality score ranges from 0 to 5 points, with 5 being the highest quality.

It appeared that two reviewers assessed validity.

Data extraction
Data were extracted to calculate relative risk (RR), risk difference (RD) and mean difference (MD), with 95% confidence intervals (CIs).

It appeared that two reviewers extracted data.
Methods of synthesis
Relative risk, standardised mean difference (SMD) and weighted mean difference (WMD), with 95% confidence intervals, were pooled by meta-analysis using a fixed-effect model. A random-effects model was used when heterogeneity was significant ($I^2 \geq 40\%$). If pooled effect estimates for dichotomous outcomes were significantly different between groups, the number needed to treat (NNT) was calculated. Heterogeneity between trials was assessed by the $I^2$ statistic.

Sensitivity analysis was performed on duration of treatment, quality of trials and sponsorship of the trial to determine whether the results of the primary outcome were robust. Subgroups were compared using the interaction test. The potential impact of unpublished trials was assessed by estimating the fail-safe number (i.e. the number of trials with non-significant results required to reverse any significant effect of inhaled corticosteroids on asthma exacerbations).

Results of the review
Eighteen RCTs (n=3,757 patients) met the inclusion criteria; although two of the trials were based on the same dataset, they were included as separate trials because they reported different outcomes. Thirteen trials compared inhaled corticosteroids and montelukast. Three trials compared inhaled corticosteroids and montelukast plus inhaled corticosteroids. Two trials evaluated inhaled corticosteroids versus montelukast versus inhaled corticosteroids plus montelukast. Eight trials were high quality (Jadad score of 4 or 5).

Patients treated for asthma with inhaled corticosteroids showed a significant decrease in risk of an asthma exacerbations compared with those treated with montelukast (RR 0.83, 95% CI 0.72 to 0.96; seven trials; n=2,429 patients; $I^2=35\%$); the number needed to treat was 24 patients (95% CI 13 to 110). These findings did not change in any of the sensitivity analyses. The fail-safe number was estimated to be 133 studies.

Children treated with inhaled corticosteroids significantly improved in pulmonary function (percentage predicted final FEV$_1$, percentage change from baseline FEV$_1$, and final morning peak expiratory flow), and clinical parameters (lower albuterol use, symptom score, rescue medication-free days, and withdrawals due to asthma exacerbations) compared with those treated with montelukast.

The addition of montelukast to inhaled corticosteroids compared with inhaled corticosteroids alone did not show any significant difference in terms of the primary and secondary outcomes (two trials).

Authors’ conclusions
Inhaled corticosteroid was significantly better for the prevention of asthma exacerbations than montelukast; evidence on the addition of montelukast to inhaled corticosteroids was inconclusive due to insufficient data.

CRD commentary
This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. The search included appropriate databases, but no apparent attempts were made to retrieve unpublished studies or review reference lists of retrieved papers, so all the relevant data may not have been included. However, the fail-safe analysis indicated that it was unlikely that publication bias could have influenced the results. To minimise errors and bias, two reviewers independently selected studies and, although not explicitly stated, it appeared that the same number of reviewers extracted data and assessed quality of the included trials.

The quality of included trials was assessed using the Jadad scale. The characteristics of the individual trials were presented. Potential sources of statistical heterogeneity were explored and reported. Sensitivity analysis demonstrated that the results were robust to changes in the factors considered.

Although there was uncertainty relating to some aspects of the reporting process, the authors’ conclusions reflected the evidence presented and appear to be broadly reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors did not state any implications for research.

Funding
None.

Bibliographic details
Castro-Rodriguez JA, Rodrigo GJ. The role of inhaled corticosteroids and montelukast in children with mild-moderate asthma: results of a systematic review with meta-analysis. Archives of Disease in Childhood 2010; 95(5): 365-370

PubMedID
19946008

DOI
10.1136/adc.2009.169177

Original Paper URL
http://adc.bmj.com/content/95/5/365.abstract

Subject indexing assigned by NLM

MeSH
Acetates /adverse effects /therapeutic use; Adolescent; Anti-Asthmatic Agents /adverse effects /therapeutic use; Asthma /drug therapy /physiopathology; Child; Child, Preschool; Drug Therapy, Combination; Forced Expiratory Volume /drug effects; Glucocorticoids /adverse effects /therapeutic use; Humans; Peak Expiratory Flow Rate /drug effects; Quinolines /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12010004780

Date bibliographic record published
20/10/2010

Date abstract record published
05/01/2011

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.