Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review

Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, Schneider A

CRD summary

The authors concluded that adding montelukast to inhaled corticosteroids (ICS) improved control of mild to moderate asthma, and that salmeterol was at least as effective as montelukast as an add-on therapy, but that montelukast may be safer long term. These conclusions may require some caution in interpretation due to the scarcity of good quality data and heterogeneity between the studies.

Authors' objectives

To evaluate the medium to long-term use of montelukast as add-on therapy to inhaled corticosteroids (ICS) in adolescents and adults with asthma, compared to ICS monotherapy or other guideline-recommended treatments.

Searching

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (all from inception to November 2006), the Cochrane Database of Systematic Reviews, DARE and the Health Technology Assessment Database were searched. Search terms were provided. The reference lists of articles retrieved were handsearched. Online clinical trial registries and databases and the websites of the European Medicines Agency and the USFDA were also searched. The manufacturers of montelukast and salmeterol were approached for additional data. Studies were required to be in English, German, Dutch, French, Spanish or Portuguese.

Study selection

Randomised controlled trials (RCTs) of montelukast as add-on therapy to ICS were eligible for inclusion provided they were conducted among adolescents and adults (aged over 12 years) with mild to moderate asthma. Studies were required to report at least one of the following outcomes: asthma symptoms, exacerbations (with or without emergency treatment), hospital admission and/or outpatient treatment, adverse effects, activities of daily living, disease-related quality of life, treatment satisfaction, physical capacity or asthma related/all-cause mortality. Trials of less than 12 weeks' duration were excluded. Trials in which more than 20 per cent of participants had severe asthma were excluded from the main analysis: severe asthma was defined as a baseline forced expiratory volume in one second (FEV_1) of 60 per cent or less of predicted value.

The mean age of participants in the included studies was 38 to 45 years. Males comprised 38 per cent to 62 per cent of study samples. Mean FEV_1 at baseline was 70 per cent to 99 per cent of predicted value. All studies included a run-in phase of one to seven weeks. All studies used a 10 milligram dose of montelukast. ICS agents included fluticasone, beclomethasone and budesonide. ICS doses varied and were either constant or tapered, with tapering regulated either by a predefined protocol or by clinical asthma scores. Control interventions included ICS monotherapy (with or without placebo) and ICS with salmeterol add-on therapy. Beta-2 agonists were permitted in all studies (where stated). Outcomes measures differed widely. Treatment duration varied from 12 to 48 weeks.

Two reviewers independently selected potentially eligible trials. Final selection was discussed with three other authors and disagreements were resolved by consensus.

Assessment of study quality

The following validity criteria were considered: design, randomisation, allocation concealment, blinding of patients and investigators, sample size estimation, complete description of dropouts and analysis by intention to treat. Two authors conducted the validity assessment.

Data extraction

For dichotomous outcomes, relative risks (RRs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs); or else percentages and p values were reported. For continuous outcomes, mean differences between the groups and standard errors were reported, with p values.

Results were reported in a table with graphics (arrows) indicating the direction of effect of each comparison and whether findings were statistically significant. Data were extracted by two authors using a standardised format.

Methods of synthesis

Studies were combined in narrative synthesis, grouped by comparison. In addition, some dichotomous data were pooled using the Mantel-Haenszel fixed-effect model to calculated pooled RRs and 95% CIs. Heterogeneity was assessed with the I^2 statistic. Subgroup analyses were conducted to test whether study duration affected outcomes. Sensitivity analyses were conducted to test the effect of adding in studies in which more than 20 per cent of participants had severe asthma.

Results of the review

Thirteen RCTs were included, 12 of which were fully published (n=5,993, range 30 to 1,490). Six studies had minor or no methodological deficiencies and seven had major deficiencies that challenged their conclusions (such as inadequate randomisation and allocation procedures, missing sample size calculations, incomplete description of dropouts and lack of ITT analysis).

Montelukast as add-on to ICS (seven RCTs, two good quality; n=1,546)

Relevant data were scarce. In studies involving constant dose ICS, symptom control was significantly better in the montelukast than the monotherapy group on a range of study-specific measures and exacerbations were reduced significantly. There was no difference between the groups with respect to quality of life, treatment satisfaction or adverse events (two RCTS, one good quality, for each comparison). In a good quality RCT involving tapered-dose ICS, the tolerated dose of ICS at endpoint was significantly lower in the montelukast group (536 versus 727 micrograms daily, p=0.046).

Montelukast versus salmeterol as add-on for constant dose ICS (six RCTs, four good quality; n=4,447)

Most individual RCTs reported significantly improved outcomes for the salmeterol group with respect to asthma symptoms and/or exacerbations (six RCTs). Pooling of two 12-week RCTs (one good quality) found a significant increase in asthma exacerbations in the montelukast group (RR 2.03, 95% CI: 1.23, 3.37, p=0.006). However, pooling of two good-quality 48-week RCTs found no significant difference between the groups for this outcome (RR 1.12, 95% CI: 0.96, 1.30). Overall adverse event rates were comparable in the two groups, but the two good-quality 48-week studies found a significantly higher rate of serious adverse events in the salmeterol group (RR 0.68, 95% CI: 0.49, 0.94, p=0.021).

No statistical heterogeneity was detected in any analysis. (I^2=0)

Results of sensitivity analyses and further results of individual studies were also reported in the review.

Authors' conclusions

Adding montelukast to inhaled corticosteroids (ICS) improved control of mild to moderate asthma. Salmeterol was at least as effective as montelukast as an add-on therapy, but montelukast may be safer long term.

CRD commentary

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for published and unpublished studies, although there was some restriction by language. Steps were taken to minimise the risk of bias and error by having more than one reviewer independently undertake study selection. Multiple reviewers were also involved in data extraction and validity assessment, but it was unclear whether they worked independently. Detailed information was provided about the included studies. Rigorous criteria were used to assess study validity and the results of the assessment were taken into account when interpreting review findings. There was marked heterogeneity in the range of outcome measures reported, though (as the authors noted) the direction of effect showed consistent trends. Appropriate statistical techniques were used to pool the few data suitable for meta-analysis, assess for heterogeneity and explore the effects of differences in study duration and asthma severity. The review was generally well conducted but the authors' conclusions may require some caution in interpretation due to the scarcity of good quality data and heterogeneity between the studies, which precluded meta-analysis in most cases.

Implications of the review for practice and research

Practice: the authors stated that montelukast should be considered as an option for add-on treatment in patients suboptimally controlled with ICS.

Research: the authors stated that studies were needed to evaluate the long term efficacy and safety of alternative controlled medications for mild to moderate asthma, taking into account factors such as patient age, ethnicity, comorbidity, patient acceptance and compliance with oral (versus inhaled) therapy. Future studies of the ICS-sparing effects of montelukast should use comparable protocols and include a prolonged run-in period to taper ICS to the minimum effective dose, with tapering regulated by asthma scores. The authors also suggested that asthma treatment guidelines should be reassessed.

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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.