NICE National Institute for Health and Care Excellence

Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Asthma in children and adolescents: leukotriene receptor antagonists

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A Cochrane review has found inconclusive evidence to support adding a leukotriene receptor antagonist to an inhaled corticosteroid at step 3 for children and adolescents aged 6-18 years with mild to moderate asthma. Until studies are published that show that they improve patient-oriented outcomes such as exacerbations requiring oral corticosteroids, prescribers should continue to follow the NICE-accredited BTS/SIGN guideline on the management of asthma which recommends a limited role for leukotriene receptor antagonists in children and adolescents aged 5 years and above.

Overview and current advice

The NICE-accredited BTS/SIGN guideline on the management of asthma recommends a stepwise approach to managing asthma in adults and children. Inhaled corticosteroids (ICS) at step 2 are recommended as the first-choice regular preventer therapy for adults and children with asthma. Leukotriene receptor antagonists may provide an alternative option for children under 5 years where ICS cannot be used. The dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained. When asthma is inadequately controlled at step 2, add-on therapy (step 3) should be considered after rechecking adherence, inhaler technique and eliminating trigger factors. For children aged less than 5 years, first choice add-on therapy is a leukotriene receptor antagonist. For adults, and children (aged 5 to 12 years) first choice add-on therapy is a long-acting beta2 agonist (LABA). Where there is no response to a LABA, the guideline recommends that the LABA is stopped and the dose of ICS is increased. If asthma control still remains inadequate after these steps then sequential trials of other add-on therapies are recommended including leukotriene receptor antagonists, theophylline and slow-release beta2 agonist tablets (adults only).

A previous systematic review and meta-analysis (Castro-Rodriguez JA, Rodrigo GJ 2010)[1] of randomised controlled trials (RCTs) compared the efficacy of ICS with a leukotriene receptor antagonist (montelukast) alone or added to ICS in schoolchildren and adolescents with mild to moderate persistent asthma. The study found ICS were statistically significantly more effective than montelukast for preventing severe asthma exacerbations requiring systemic corticosteroids.

See the Clinical Knowledge Summaries (CKS) topic page and NICE Evidence topic page on asthma for a general overview of this condition.

New evidence

A Cochrane systematic review[2] (which replaces an earlier review that included mainly studies in adults[3]) has examined the efficacy and safety of the combination of leukotriene receptor antagonists and ICS, compared with the same dose, or an increased dose of ICS in children and adolescents with persistent asthma who remain symptomatic despite maintenance use of ICS.

Four published RCTs (n=559) including children and adolescents aged 6 to 18 years, with mild to moderate asthma, provided data for the review. The leukotriene receptor antagonist used in all of the trials was montelukast at a dosage of 5 mg once daily for children aged 6 to 14 years, and 10 mg once daily for adolescents aged 15 years and over. Montelukast was administered for between 4 and 16 weeks in the trials.

Three of the trials compared montelukast plus ICS (budesonide) to the same dose of ICS alone. There was no statistically significant difference between the groups for the primary outcome, participants with at least one exacerbation requiring oral corticosteroids over 12 weeks (1 trial, n=268; risk ratio [RR] 0.80; 95% confidence interval [CI] 0.34 to 1.91). There was also no statistically significant difference between the groups for the secondary outcome, change in forced expiratory volume in 1 second (FEV1) from baseline (1 trial, n=251, mean difference [MD] 1.30, 95% CI −0.09 to 2.69). There was, however, a statistically significant difference between the groups in the secondary outcomes, change in morning and evening peak expiratory flow rates from baseline (1 trial, n=218, MD 9.70 L/min, 95% CI 1.27 to 18.13; and MD 10.70, 95% CI 2.41 to 18.99 respectively). There was no statistically significant difference between the groups in overall withdrawals (3 trials, n=368, odds ratio [OR] 1.93, 95% CI 0.74 to 5.05), or withdrawals due to adverse effects (1 trial, n=270, OR 0.49, 95% CI 0.04 to 5.43).

The other trial compared montelukast plus ICS (fluticasone) with a higher dose of ICS. No statistically significant difference between the groups was observed for the primary outcome, participants with at least one exacerbation requiring oral corticosteroids over 16 weeks (1 trial, n=182, RR 0.82, 95% CI 0.54 to 1.25).This was also true for the secondary outcome, participants with at least one exacerbation requiring hospitalisation (1 trial, n=182, RR 1.00, 95% CI 0.06 to 15.87). There was also no statistically significant difference between the groups in overall withdrawals (1 trial, n=182, OR 1.30, 95% CI 0.47 to 3.57). Withdrawals due to adverse effects were not reported in this trial.

Commentary provided by the NICE Medicines and Prescribing Centre

This Cochrane review[2] replaces an earlier review from 2004 where only 2 studies in children were included[3]. Since then, several studies in children have been published and the authors of the current Cochrane review hoped these would provide clarity on the role of leukotriene receptor antagonists as an adjunct to ICS in the management of asthma in children. However only 5 RCTs met the inclusion criteria and, of these, only 4 provided data for the review. In addition only 2 of these reported data on the primary outcome, namely, the number of participants requiring rescue oral corticosteroids. The only safety outcome that could be aggregated from the included trials was overall withdrawal which showed no significant differences between the groups. The authors of the review report that no serious adverse events were observed in the small studies that were included.

The review was limited as it only included trials of children aged 6 years and above and so no conclusions about the efficacy and safety of leukotriene receptor antagonists in younger children can be made. In addition all the trials used montelukast and so it is not clear whether other leukotriene receptor antagonists would give similar results. Only 4 trials provided data for the review which limits its statistical power and the confidence in the findings.

The lack of studies in children and inadequate reporting of the included studies limit the conclusions that can be drawn here. Clinicians should continue to follow the NICE-accredited BTS/SIGN guideline on the management of asthma which recommends a limited role for these drugs. Published studies showing the effectiveness of leukotriene receptor antagonists on patient-oriented outcomes are needed, particularly in younger children (less than 6 years).

Study sponsorship

This systematic review and meta-analysis was performed by the Cochrane Airways Group. The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Airways Group.

References

1. Castro-Rodriguez JA, Rodrigo GJ (2010) The role of inhaled corticosteroids and montelukast in children with mild–moderate asthma: results of a systematic review with meta-analysis. Arch Dis Child 95:365-370
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3. Ducharme FM (2004). Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. Cochrane Database of Systematic Reviews. Issue 1. DOI: 10. Art No.: CD003133. 1002/14651858.CD003133.pub2

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