Addition of antileukotriene agents to inhaled corticosteroids in children with persistent asthma

Jimmy K Chong MD PhD[1], Bhupendrasinh F Chauhan MPharm PhD[2]

For the current issue of the *Journal*, we asked Drs Jimmy Chong and Bhupendrasinh Chauhan to comment on and put into context the Cochrane Review on the efficacy and safety of adding antileukotriene agents (LTRAs) to low-dose inhaled corticosteroids (ICS) in children with persistent asthma (1).

Background

In the treatment of children with mild persistent asthma, low-dose ICS are recommended as the preferred monotherapy (referred to as step 2 of therapy). In children with inadequate asthma control on low doses of ICS (step 2), asthma management guidelines recommend adding an LTRA to existing ICS as one of three therapeutic options to intensify therapy (step 3).

Methods

Search strategy: Trials were identified from the Cochrane Airways Group Specialised Register of Trials, which is derived from systematic searches of bibliographical databases, including the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, AMED and CINAHL, and a manual search of respiratory journals and meeting abstracts, as well as the website www.clinicaltrials.gov. The search was conducted until January 2013.

Selection criteria: Randomized controlled trials (RCTs) that involved children and adolescents one to 18 years of age, with asthma, who remained symptomatic despite the use of a stable maintenance dose of ICS, and in whom LTRAs were added to ICS and compared with the same, an increased or a tapering dose of ICS for at least four weeks were considered for inclusion.

Data analysis

Sandard methods outlined by The Cochrane Collaboration were used.

Results

Five paediatric (parallel group or cross-over) trials met the inclusion criteria. Two (40%) trials were considered to be at a low risk for bias. Four published trials, representing 559 children (≥6 years of age) and adolescents with mild-to-moderate asthma, contributed data to the review. No trial enrolled preschool-age children. All trials used montelukast as the LTRA, administered for between four and 16 weeks. Three trials evaluated the combination of LTRAs and ICS compared with the same dose of ICS alone (step 3 versus step 2). No statistically significant group difference was observed in the only trial reporting participants with exacerbations requiring oral corticosteroids over four weeks (n=268 participants; RR 0.80 [95% CI 0.34 to 1.91]). There was also no statistically significant difference in percent change in forced expiratory volume in 1 s (FEV_1) in this trial, with a mean difference (MD) of 1.3 (95% CI −0.09 to 2.69); however, a significant group difference was observed in the morning and evening peak expiratory flow rates: n=218 participants; MD 9.70 L/min (95% CI 1.27 L/min to 18.13 L/min) and MD 10.70 L/min (95% CI 2.41 L/min to 18.99 L/min), respectively. One trial compared the combination of LTRAs and ICS with a higher dose of ICS (step 3 versus step 3). No significant group difference was observed in this trial for participants with exacerbations requiring rescue oral corticosteroids over a 16-week period (n=182 participants; RR 0.82 [95% CI 0.54 to 1.25]), nor was there any significant difference in exacerbations requiring hospitalization. There was no statistically significant group difference in withdrawals overall or because of any cause with either protocol. No trial explored the impact of adding LTRAs as a means to taper the dose of ICS.

Conclusions

The addition of LTRAs to ICS is not associated with a statistically significant reduction in the need for rescue oral corticosteroids or hospital admission compared with the same or an increased dose of ICS in children and adolescents with mild to moderate asthma. Although LTRAs have been licensed for use in children for >10 years, the paucity of paediatric trials, the absence of data regarding preschool-age children and the variability in the reporting of relevant clinical outcomes considerably limit firm conclusions. At present, there is no firm evidence to support the efficacy and safety of LTRAs as add-on therapy to ICS as a step 3 option in the therapeutic arsenal for children with uncontrolled asthma symptoms on low-dose ICS.

The full text of the Cochrane Review is available in The Cochrane Library (1).

EXPERT COMMENTARY

Asthma management guidelines recommend one of three available treatment options for children with suboptimal asthma control with daily low-dose ICS: increasing the ICS dose to a moderate level by doubling the dose; adding a long-acting beta-agonist (LABA); or adding an LTRA (2-4).

The presented Cochrane review of LTRAs is based on outcomes occurring over four to 16 weeks in five trials, representing 559 school-age children with poor asthma control on low-dose ICS. Authors compared addition of the LTRA (montelukast) to the low-dose ICS with continuing the low-dose ICS alone (step 2), or changing to moderate-dose ICS (step 3). The outcomes with add-on LTRA are disappointing, with no clear benefits in markers of future risk (ie, exacerbations requiring oral corticosteroids or hospital admission), withdrawals and adverse events. The only moderate benefit was in the morning

[1]*University of Auckland, Auckland, New Zealand;* [2]*CHU Sainte-Justine, Montreal, Quebec*

Correspondence: Dr Bhupendrasinh F Chauhan, Clinical Research Unit on Childhood Asthma, CHU Sainte-Justine, 3175 Chemin de la Côte-Sainte-Catherine, Office A-836, Montreal, Quebec H3T 1C5. Telephone 514-345-4931 ext 4997, fax 514-345-4872, e-mail bchauhan28@gmail.com

Accepted for publication July 19, 2014

and evening peak expiratory flow rate (MD 9.70 L/min [95% CI 1.27 L/min to 18.13 L/min] and 10.70 L/min [95% CI 2.41 L/min to 18.99 L/min], respectively) (1). Moreover, the results may not be applicable to preschool-age children, and no comments can be made as to the long-term safety of LTRA+ICS with regard to lung growth due to the paucity of long-term paediatric trials. Montelukast (Singulair; Merck, USA) and its generics are the only approved LTRAs in the Canadian market, and cost approximately $29 to $91 per month (5).

The alternative option of add-on LABA to existing daily low-dose ICS is very well evaluated. In a Cochrane review, the LABA+ICS, compared with the same dose of ICS (step 2), failed to show superiority in the rate of exacerbation requiring systemic steroids, but significantly increased FEV_1 (0.08 L [95% CI 0.06 L to 0.11 L]). Similarly, compared with double-dose ICS (step 3), the LABA+ICS did not significantly reduce the risk of exacerbations requiring systemic steroids but, again, significantly improved morning and evening peak expiratory flow (MD 7.55 L/min [95% CI 3.57 L/min to 11.53 L/min] and 5.5 L/min [95% CI 1.21 L/min to 9.79 L/min]) (6). In fact, the trend toward increased risk of exacerbations requiring oral steroids and hospital admissions in children on LABA+ICS compared with double-dose ICS (step 3) raised safety concerns in children <12 years of age (7).

ICS demonstrate a dose-response relationship for both efficacy and safety (as determined by growth velocity); however, most of the benefit is gained with low-to-moderate ICS dose, with minimal benefit in further increasing the dose (8,9). The approach of increasing the dose of ICS from low to moderate is often more practical than adding either LABA or LRTA because the inhaler has already been purchased. Consistent with this, the Canadian asthma management guideline recommends increasing the dose of ICS over add-on options in children with suboptimal asthma control with low-dose ICS (3).

To our knowledge, no overview comparing the three treatment options in paediatric populations has been published to date, although this would be complicated by the heterogeneity of the patients enrolled in the different trials. A recent study published after the previously noted Cochrane reviews (6,7) evaluated school-age children with uncontrolled asthma despite the use of low-dose ICS (10). Overall, outcomes were best with LABA step-up (in terms of acute exacerbation requiring oral steroid, asthma control days and FEV_1). However, certain individuals responded better to increased ICS dose or add-on LTRA, indicating the importance of various factors (age, sex, race, type of chronic inflammation, polymorphism, environmental exposure, etc) influencing the magnitude of treatment response and the need for personalized treatment. Considering the paucity of paediatric trials, we recommend further high-quality trials (especially involving preschool-age children) combined with an overview to confirm which treatment approach should be preferred.

REFERENCES

1. Chauhan BF, Ben Salah R, Ducharme FM. Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma. Cochrane Database Syst Rev 2013;(10):CD009585.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2014. <www.ginaasthma.org> (Accessed August 12, 2014).
3. Lougheed MD, Lemiere C, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update. Diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 2012;19:127-64.
4. British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. A national clinical guideline. (SIGN publication no. 101). <www.sign.ac.uk/guidelines/fulltext/101/index.html> (Accessed September 10, 2012).
5. Merck & Co, Inc. Singulair (montelukast sodium) tablets, chewable tablets, and oral granules prescribing information. Whitehouse Station: Merck & Co, Inc, August 2009.
6. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009;(3):CD007949.
7. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting $beta_2$-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010;(4):CD005533.
8. Adams NP, Jones PW. The dose-response characterisitcs of inhaled corticosteroids when used to treat asthma: An overview of Cochrane systematic reviews. Res Med 2006;100:1297-306.
9. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SOM, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: Dose-response effects on growth. Cochrane Database Syst Rev 2014;(7):CD009878.
10. Lemanske RF, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med 2010;362:975-85.

The Evidence for Clinicians columns are coordinated by the Child Health Field of the Cochrane Collaboration (www.cochranechildhealth.org). To submit a question for upcoming columns, please contact us at child@ualberta.ca.