JOURNAL ROUND-UP<http://www.thepcrj.org>**Treatment of preschool asthma with leukotriene receptor antagonists: what's new?**

C.P. Onno van Schayck*

Professor of General Practice, Research Institute CAPHRI, University of Maastricht, PO Box 616, 6200 MD Maastricht, The Netherlands

*Tel: +31 43 388 2152

E-mail address: Onno.vanSchayck@HAG.unimaas.nl

The greatest prevalence of asthma is in preschool children. However, it is difficult to identify those preschool children with early onset wheeze who have airway inflammation which requires anti-inflammatory medication.¹ Inhaled corticosteroids (ICS) have not been shown to change the development of asthma symptoms or to change lung function in this age group,²⁻⁴ although some high-risk groups (especially highly atopic children) might have immediate benefit during treatment with inhaled steroids.⁵ Early reports with the orally-administered leukotriene receptor antagonist (LTRA) montelukast in preschool children showed that this drug might control asthma symptoms,⁶ provide clinically relevant bronchoprotection,⁷ and/or reduce lung symptoms subsequent to RSV bronchiolitis.⁸ Recently, two long-term studies have investigated the role of LTRAs in mild intermittent preschool asthma, a population which is particularly relevant for primary care. These two studies are reviewed here. Bisgaard *et al.* investigated the prevention of viral-induced asthma exacerbations by continuous treatment with montelukast, whilst Robertson *et al.* have studied the effect of intermittent montelukast use on the severity of an asthma episode.

Bisgaard H, Zielen S, Garcia-Garcia ML, *et al.* Montelukast reduces asthma exacerbations in 2-5 year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171:315-22.

Objective: The PREVIA study was designed to investigate the role of montelukast in the prevention of viral-induced asthma exacerbations in children aged 2 to 5 years with a history of intermittent asthma symptoms.

Methods: The study was a 12-month multi-centre, double-blind, parallel-group study of patients with asthma exacerbations associated with respiratory infections and minimal symptoms between episodes. Patients were randomised to receive oral montelukast 4 or 5 mg (depending on age) (n = 278) or placebo (n = 271) once a day for 12 months.

Measurements and Main Results: Caregivers recorded children's symptoms, beta-agonist use, and health care resource use in a diary card. Over 12 months of therapy, montelukast significantly reduced the rate of asthma exacerbations by 31.9% compared to placebo. The average rate of exacerbation episodes per patient was 1.60 episodes per year on montelukast compared to 2.34 episodes on placebo. Montelukast also delayed the median time to first exacerbation by approximately 2 months (p=0.024), and the rate of inhaled corticosteroid courses (p=0.027) compared to placebo.

Conclusions: Montelukast effectively reduced asthma exacerbations in 2- to 5-year-old patients with intermittent asthma over 12 months of treatment and was generally well tolerated.

Robertson CF, Price D, Henry R, *et al.* Short-course montelukast for intermittent asthma in children. A randomized controlled trial. *Am J Respir Crit Care Med* 2007;175:323-9.

Rationale: In children, intermittent asthma is the most common pattern and is responsible for the majority of exacerbations. Montelukast has a rapid onset of action and may be effective if used intermittently.

Objectives: To determine whether a short course of montelukast in children with intermittent asthma would modify the severity of an asthma episode.

Methods: Children, aged 2-14 years with

intermittent asthma participated in this multi-centre, randomised, double-blind, placebo-controlled clinical trial over a 12-month period. Treatment with montelukast or placebo was initiated by parents at the onset of each URTI or asthma symptoms, and continued for a minimum of seven days or until symptoms had resolved for 48 hours.

Measurements and Main Results: 220 children were randomised, 107 to montelukast and 113 to placebo. There were 681 treated episodes (345 montelukast, 336 placebo) in 202 patients. The montelukast group had 163 unscheduled healthcare resource utilisations for asthma compared to 228 in the placebo group (AR 0.65 (95% CI 0.47-0.89)). There was a non-significant reduction in specialist attendances and hospitalisations, duration of episode, β -agonist and prednisolone use in the montelukast group. Symptoms were reduced by 14% and nights awake by 8.6% ($p=0.043$), days off from school or childcare by 37%, and parent time off from work by 33% ($p<0.0001$ for both).

Conclusions: A short course of montelukast, introduced at the first signs of an asthma episode, results in a modest reduction in acute health care resource utilisation, symptoms, time off from school, and parental time off from work, in children with intermittent asthma.

Commentary

Leukotrienes are important inflammatory mediators in the pathophysiology of asthma. They stimulate bronchoconstriction, mucus secretion, vascular permeability, and the mobilisation of eosinophils. LTRA drugs specifically counteract leukotriene inflammatory mediators, in contrast to ICS which have other anti-inflammatory properties.

Some aspects of LTRA activity are of particular importance in children. LTRAs have been shown to be effective against virally-induced asthma in young children; asthma complaints and the number of exacerbations in children clearly fall during use of LTRAs. It is important in children that LTRAs appear to be effective in protecting against bronchial hyperreactivity resulting from cold air provocations.⁷ In line with this, they have been shown to be effective in exercise-induced bronchoconstriction.⁹ The once-a-day oral administration of montelukast seems to lead to greater compliance and satisfaction amongst parents than the use of inhaled corticosteroids, which have to be taken several times a day.^{10,11}

However, in direct comparative studies with

ICS, LTRAs have been shown to be less effective in improving pulmonary function, asthma symptoms, quality of life, asthma attacks, rescue medication and asthma-related costs in asthmatic children older than 6 years of age.^{12,13} A Cochrane review of 27 studies in both children and adults confirmed the superior role of ICS compared to LTRAs in asthma.¹⁴ This is the reason that LTRAs are described in international guidelines such as GINA¹⁵ as an additive treatment to ICS instead of an alternative to ICS in both adults and children.

Yet, no comparative studies are available in children under the age of 6, and the response to ICS in these children is poor,^{2,5} certainly in comparison with LTRAs in this age group, as per the studies reviewed here. We obviously need direct comparative trials before drawing any conclusions, but it is tempting to speculate why LTRAs may be more effective in children under the age of 6.

Children in this age group often present intermittent symptoms, mostly induced by common colds, and can have an increased susceptibility to respiratory infections. Viral infections are the main cause of early childhood asthma exacerbations, while leukotrienes (such as LTC₄) play a crucial role in viral-induced wheeze.¹⁶ In the study by Bisgaard *et al.* virus (mostly rhinovirus) was identified in almost half of the exacerbations. A non-significant reduction of 29% was observed in children treated with LTRA compared to placebo in a subsample of the patients. In contrast, a Cochrane review on the effect of ICS in children with viral-induced intermittent asthma did not show any effect on the frequency of wheezing episodes.¹⁷ This difference in effect between LTRAs and ICS on viral-induced exacerbations could explain the differences in effect on asthma of these drugs in early infancy. However, again no conclusions can be drawn before direct comparative trials are performed.

Robertson *et al.* showed that the relatively rapid onset of clinical benefit from LTRAs within 24 hours makes it possible to use a short course of montelukast at the first sign of rhinitis or asthma symptoms in order to modify the severity of the asthma episode. The consequence is that the total number of unscheduled visits to the GP, paediatrician, emergency department or admission to hospital was reduced by almost 25%, while absence from school or childcare was reduced by 37%. Interestingly, there is now some evidence that ICS do work when given as a short course in preschool asthma,¹⁸ but again, we need more comparative trials between LTRAs and ICS in this specific age group.

In conclusion, LTRAs are drugs which

specifically counteract leukotriene inflammatory mediators. ICS have other anti-inflammatory properties, and LTRAs are effective additive anti-inflammatory drugs, especially in children with uncontrolled asthma on ICS alone. In preschool children, LTRAs have been shown to be relatively effective in reducing viral-induced exacerbations and unscheduled health care resource utilisation, while ICS have shown disappointing effects thus far. However, no conclusions on drug superiority in this specific age group can be drawn before direct comparative trials have been performed.

Conflict of interest declaration

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Treatment of preschool asthma: two new LTRA placebo-controlled trials

Marianne Stubbe Østergaard

Associate Professor, Department of General Practice, University of Copenhagen, Øster Farimagsgade 5-Q, DK 1014 K, Denmark

Tel: +45 45 50 51 00

E-mail: m.stubbe@gpmmed.ku.dk

In preschool children, intermittent asthma is a common pattern. Viral infections are the main cause of early childhood asthma exacerbations. Generally, inhaled corticosteroids (ICS) are recommended as the first-line drug of choice for childhood asthma.¹ However, drugs other than ICS – such as leukotriene receptor antagonists (LTRAs) – may be alternatives or additives in different age groups, particularly when ICS are not available.

In schoolchildren, direct comparisons between ICS and LTRAs have demonstrated ICS to be superior and cheaper for children aged 4 to 17 years.² Also, ICS was more favorable than an LTRA in terms of clinical and pulmonary outcomes as well as anti-inflammatory response in children