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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

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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

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aged 6-17 years.[3] A Cochrane review concluded that there was superiority of ICS compared to LTRA in school children and adults.[4] Both ICS monotherapy and ICS in combination with long-acting beta-agonist (LABA) achieved greater improvements than LTRA in asthma control.[5]

However, in children exclusively under the age of 6, no direct comparative studies between ICS and LTRAs are available. In preschool children, episodic high dose ICS has proved to be effective for treating acute episodes of asthma, with no clinically-relevant systemic effects.[6]

Recently, two placebo-controlled studies of LTRA in mild intermittent preschool (and school) asthma have been published — as reviewed above. The study by Robertson *et al*.[7] — on a short course of montelukast for intermittent asthma in children aged 2-14 years — demonstrated a relatively rapid effect within 24 hours. Symptoms were reduced by 14%, the number of nights awake was reduced by 8.6% compared to placebo, and the study found a modest, but non-significant reduction in health care utilisation, beta-agonist and prednisolone use. Bisgaard *et al*.[8] investigated the prevention of viral-induced asthma exacerbations in 2-5 year-old children by continuous treatment with montelukast. Over 12 months of therapy, montelukast significantly reduced the rate of asthma exacerbations by 31.9% compared to placebo, and reduced the rate of inhaled corticosteroid courses compared to placebo (p=0.027).

Commentary

These two studies, together with other preschool placebo-controlled LTRA studies,[9,10] demonstrate that montelukast has a place in the treatment of preschool asthma.

It is risky to compare and speculate about different placebo-controlled studies, because they operate with different definitions, designs, sizes, statistics etc. However, looking solely at these two new LTRA studies, and ignoring the solid body of evidence regarding the role of ICS in preschool children, including two reviews,[6,11] would be a mistake.

Episodic short-term high dose ICS induces a rapid clinical response in intermittent asthma/recurrent wheezing.[12-16] However, it is important to stress that episodic low or moderate doses of ICS in children with intermittent wheezing did not prove effective.[17] In persistent severe asthma, continuous ICS in preschool children significantly reduced asthma exacerbations, asthma symptoms, and rescue beta-2-agonist and oral steroid use, and was well tolerated with no clinically relevant systemic effects.[18,19] However, no definite conclusions can be drawn on drug superiority in the under-6 age group until direct comparative trials have been performed.

GINA proposes an LTRA as one of several possible add-on/steroid-sparing drugs in treating childhood asthma. In fact, there is a need here for direct comparative add-on studies in children comparing LTRAs, beta-agonists, and the xanthines (e.g. theophylline) — which seem to have some potential as oral add-on therapy.[20] Already some comparative trials give us guidance: in direct comparison, a LABA was found superior to an LTRA as add-on therapy to ICS for chronic asthma;[21] and 400 mcg budesonide was shown to be superior to 200 mcg budesonide plus 5 mg of oral montelukast in children.[22]

In conclusion, what is needed in infants and preschool children with asthma is direct comparative studies between possible first-line treatments and add-on therapies — including studies on ICS, beta-agonists, LTRAs and xanthines. Preferably these trials should be in the primary care setting.

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Conflict of interest declaration

There are no conflicts of interest to declare.

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