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Mini-Sympoisum: Childhood asthma: The fuss and the future

# Montelukast in paediatric asthma: where we are now and what still needs to be done?☆

Andrew Bush *

*Professor of Paediatrics and Head of Section (Paediatrics), Imperial College, Professor of Paediatric Respirology, National Heart and Lung Institute, Consultant Paediatric Chest Physician, Royal Brompton Harefield NHS Foundation Trust*

**EDUCATIONAL AIMS**

The reader will come to appreciate that:

- The use of leukotriene receptor antagonists in asthma management is commonplace and likely excessive.
- The clinical response to montelukast varies considerably and unpredictably in children, reinforcing the need for better biomarkers in the management of asthma.
- Those most likely to benefit from montelukast would appear to be younger, less atopic children with milder, in particular episodic symptoms.

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SUMMARY

Leukotriene receptor antagonists were introduced as an entirely new concept in asthma therapy, which indeed they are. However, although an intellectually new concept, they have largely disappointed in clinical practice. A small minority of school age asthmatics may respond better to these medications as against inhaled corticosteroids as prophylactic therapy. In children not responding to low dose inhaled corticosteroids, the best add-on therapy is salmeterol, but a small number respond better to Montelukast. In pre-school wheeze, intermittent Montelukast may be an effective strategy in some children who wheeze just with viral colds, but the clinical trial data are controversial. Pre-schoolers with multiple trigger wheeze are probably best treated with inhaled corticosteroids. What is clear is that clinically, a higher proportion of children are prescribed Montelukast than would be predicted from the literature to respond to the medication. No biomarker to predict response to Montelukast has reached clinical practice, so N of 1 clinical trials should be performed. It is important not to leave children on Montelukast if there is no convincing response to this treatment.



## INTRODUCTION

Leukotriene receptor antagonists (LTRAs) were (rightly) hailed as a whole new and novel class of asthma medications, distinct from the steroid based therapies and short and long acting β-2 agonists. However there is all the difference in the world between an intellectually interesting concept and a therapeutic great leap forward. It is probably fair to say that the latter has not been delivered. The aim of this manuscript is to review the current positioning of montelukast in the context of pre-school wheeze and childhood asthma; and, given the current uncertainties in the treatment role of montelukast, to propose both mechanistic and clinical ways forward.

## ROLE OF LTRAS IN SCHOOL AGE ASTHMA

A Cochrane review of every rigorously conducted, head to head comparison between LTRAs and inhaled corticosteroids (ICS) came down unequivocally for the superiority of ICS [1]. It is true that a

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* Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. Tel.: +207-351-8232; fax: +207-351-8763.
*E-mail address:* a.bush@imperial.ac.uk.

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so-called 'real life study' has reported equivalence [2]. However, such studies often lack rigour; how many children actually needed any treatment? By definition, two unnecessary treatments will be equally (un)efficacious; likewise, if patients are equally uncompliant with two different treatments, they are likely to be indistinguishable in terms of outcomes. Indeed, the notion that adherence to a tablet is likely to be better than to an inhaler is, like so many ideas about adherence, likely fallacious [3]. So for example, one head to head comparison recruited 144 children aged 6-17 years, of whom 17 dropped out, with mild-moderate persistent asthma [4]. They used two different crossover regimes, of treatment with either fluticasone or montelukast, of eight weeks each. The end-point was an improvement of first second forced expired volume ($FEV_1$) of more than 7.5%. Given the relatively poor utility of spirometry in school age asthma [5–7], this could have been criticised with the benefit of the retrospectoscope (as with so many studies with such a useful instrument!). However, they reported similar findings with other endpoints, and also suggested that high exhaled nitric oxide (FeNO) might be a good predictor of response to fluticasone [8]. Nonetheless, they reported that 55% did not respond to either medication, and 17% responded to both. Of those who differentially responded to a single medication, 5% responded to montelukast and 23% to fluticasone. Overall, 24 children had a better $FEV_1$ response with montelukast therapy, compared to 75 with fluticasone. The differential responses were related to biomarkers at baseline. A favourable response to fluticasone, as against non-responders, was associated with a high FeNO, higher blood eosinophil count, and elevated serum sIgE and eosinophilic cationic protein (ECP). A favourable fluticasone response was also associated with a lower Methacholine $PC_{20}$ ($PC_{20}$meth) and worse spirometry. A favourable response to montelukast, as against non-responders, was seen in younger children, with a shorter disease duration; it is speculative that these might have been children with episodic viral wheeze (EVW). A differential better response to fluticasone as against montelukast was associated with greater use of bronchodilators and a better response, a greater FeNO and serum ECP, worse spirometry and a lower $PC_{20}$meth. Overall, fluticasone seemed to be the treatment of choice if spirometry was low and airway inflammation marked. The issue of biomarkers for differential response has been taken further in subsequent studies (below). What has not been tested in this or any other study is whether this sort of differential response is consistent within an individual over time.

The BADGER study addressed the important question of how best to manage the asthmatic child who remains symptomatic despite being prescribed (and inhaling!) 100 mcg fluticasone twice daily [9]. The options tested in a triple crossover design were adding either the long acting the β-2 agonist salmeterol, or montelukast, or increasing the dose of ICS to 250 mcg bd. FeNO, $PC_{20}$meth, beta-receptor polymorphisms and the asthma control test (ACT) were used as prospective biomarkers to predict response. The salient features of the results were (a) that the most successful strategy was the addition of salmeterol; (b), and disappointingly for the lovers of biomarkers, responders to salmeterol were predicted by an ACT of >19/25; and (c) that for most children, the plateau of the dose response curve was at the surprisingly low dose of 200 mcg/day. Although some children responded to the addition of montelukast, it was clear that for many, this was not a successful strategy. Subsequent reports also suggested that salmeterol was the best add-on therapy in children without eczema. In children with eczema there were racial differences in optimal step-up therapy, although, as the authors rightly conclude, the data are hypothesis-generating and need to be replicated in another population [10]. They also showed that impulse oscillometry predicted a better $FEV_1$ response to salmeterol, but that there was a non-significant trend ($p = 0.053$) to urinary LT-$E_4$ levels predicting a better response to montelukast. Again, these results have to be considered hypothesis-generating and requiring confirmation [11].

In summary, montelukast in large groups of school age children is inferior to ICS as a first line preventer and inferior to LABA as add-on therapy. Clinical experience is that some individuals may benefit, but we do not know how to select them prospectively. Clinical experience is also that many children are left on leukotriene receptor antagonists long term with no evidence of benefit, and no deterioration on stopping treatment.

## ROLE OF LTRAS IN PRE-SCHOOL AGE WHEEZE

Numerous guidelines have stressed the phenotypic dissimilarity between at least some pre-school wheezing syndromes and school age asthma [12,13]. Episodic (viral) wheeze (EVW) is defined as wheeze in association with a (usually) clinically diagnosed viral upper respiratory tract infection (URTI); it is not synonymous with any of the transient early wheeze syndromes.

Multi-trigger wheezers wheeze both with viral URTI and also other triggers between URTIs, such as excited behaviour and allergen exposure. It should be noted that it is not the same as persistent wheeze. There is independent pathological support for this classification; MTW but not EVW children have eosinophilic inflammation on airway biopsy [14] and MTW worse airflow obstruction and a higher FeNO [15]. It should be noted in passing that these phenotypes may vary with time and the child should be re-evaluated regularly. In terms of treatment of pre-school wheeze, we have no disease modifying therapies; at least three good studies [16–18] have shown that early institution of ICS treatment even in those with a higher risk of developing asthma (positive modified asthma predictive index [19]) does not reduce the risk of the subsequent development of asthma, so treatment should be based on symptoms.

Three studies have addressed the question as to whether intermittent montelukast is effective in treating pre-school wheeze [20–22]. The PREEMPT study [20] compared intermittent montelukast with placebo (>100 children and >300 exacerbations/group). The benefit was in the youngest children, and there was around a one third reduction in the time the child was removed from a childcare facility and the time the carer was off work. A North American study [21] in 238 pre-school children compared intermittent nebulised budesonide (the only aerosolised steroid permitted by the FDA), intermittent montelukast and placebo, given at the time of a viral-induced exacerbation. There were minor and equivalent benefits for montelukast and budesonide over placebo, but the end-points were rather soft and the results not dramatic. The largest study of all [22] recruited intermittently wheezing children age 6/12 to 5 years; 589 were treated with daily Montelukast, 591 with intermittent Montelukast, and 591 with placebo. The primary end-point was episodes culminating in an asthma attack. There were a mean of 4 exacerbations/child, and therefore more than 2000 exacerbations/group. There was no improvement in the primary end-points, but statistically significant numerical improvements in some $2^{ry}$ end-points; however this must be considered a negative study. The ALOX study [23] is the subject of another manuscript in this mini-symposium, but does not alter my conclusions as to the role of montelukast in pre-school wheeze.

So where if anywhere should we position montelukast in the treatment of pre-school wheeze? Clearly it will not work for all children, but clinical experience is that there are a sub-group for whom this treatment is dramatically effective; and it should be noted that there are few dramatic therapeutic successes in this context. I suggest that, whereas ICS are first line preventive