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

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

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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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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 (FEV₁) 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 18% 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 FEV₁ 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 PC20 (PC20meth) 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 PC20meth. 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 β-2 agonist salmeterol, or montelukast, or increasing the dose of ICS to 250 mcg bd. FeNO, PC20meth, 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 disappointing 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 FEV₁ response to salmeterol, but that there was a non-significant trend (p = 0.053) to urinary LT-E4 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 including 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 2nd 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 does anyone else 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
treatment for MTW, especially if the child is atopic [24], montelukast can be positioned as first line ‘preventive treatment’ in EVW in pre-school children, provided that preventive treatment is justified by the symptoms. I would trial montelukast intermittently with viral colds as first line therapy. If that does not work, I would next go to continuous therapy, especially in children who have a pattern of very rapid deterioration. I always use a three step protocol to ensure that any apparent improvement is not due to the natural history of the disease (Text Box). Although in the main, montelukast is a very safe medication, it is essential to warn parents about potential behavioural side-effects. These are rare but alarming, but fortunately recover if treatment is stopped.

**HOW DO WE MOVE FORWARD?**

It is clear that Montelukast has at best a role in a minority of asthmatics at any age. This was confirmed in an adult study of really severe asthma [25]; 100 adult asthmatics were recruited. They were prescribed ICS 250-4000mcg (Fluticasone equivalent) and the data were analysable in 91. The protocol was 2 weeks Montelukast/Placebo, followed by 2 weeks wash out, and then 2 weeks Placebo/Montelukast in random order. There was an independent statistical analysis. There was absolutely no discernable benefit. Nonetheless, every series reporting really severe asthma includes numerous patients who continue to take Montelukast. So for example, in the SARP study, a minimum of 67% of their cluster 5 (fixed airflow obstruction) and 54% of cluster 3 (obese, very late onset) were using Montelukast [26]! In two papers from our group [27,28] 50/102 (49%) and 31/53 (58%) were prescribed Montelukast. It is inconceivable from the literature that all these patients are getting benefit. Anecdotally, many patients are able to stop Montelukast without any deterioration. More likely, equivocal transient benefit was noted and the physician did not have the courage to discontinue therapy in a symptomatic patient. It would seem to be good practice to use the six week, three stage protocol above in clinical practice; unfortunately, the lack of availability of placebo precludes this. Perhaps legislators should consider mandating the availability of placebos and this sort of trial for some medications in the future.

If the ideal of a placebo controlled, therapeutic trial is not attainable, what about biomarkers to predict response? Despite a number of attempts in big groups, no biomarker has met the twin criteria of being validated in a second cohort and reaching routine clinical practice. A re-analysis of the PACT trial reported on 191 children, median age 9.5 years, who were prescribed either fluticasone 100 mcg bd or Montelukast 5 mg od [29]. Potential predictors which were studied were age at onset of symptoms and diagnosis of asthma; presence of atopy; IgE levels; bronchial hyper-responsiveness; blood eosinophil count and ECP; and urinary LTE4. The authors concluded that the best predictors of ICS response ‘might’ be a history of parental asthma, an increased FeNO, a low PC20 and previous ICS use. This was taken further in a study of 318 asthmatic children enrolled in CLIC & PACT [30], both as a combined cohort and separate analyses of the two studies. The relationship between urinary LTE4:FeNO ratio and spirometry and asthma control days was determined; an elevated LTE4:FeNO ratio (analysing both cohorts together) associated with better Montelukast response for FEV1 and asthma control days. The authors found that those with a ratio >75th percentile were more likely to be younger, female, less atopic, and have a higher higher methacholine PC20. However, this has yet to be validated in another large group, which needs to be done before it can be recommended to be utilised in clinical practice.

The suggestion has been made that children with asthma and allergic rhinitis as a co-morbidity may respond better to montelukast than children with asthma alone. It is clear that allergic rhinitis should be treated on its own merits, since it causes considerable morbidity [31]. Furthermore, in terms of upper airway disease, Montelukast may have a role in treating mild sleep disordered breathing and obstructive sleep apnoea [32]. However, there is no evidence that allergic rhinitis as a co-morbidity predicts a better response to Montelukast.

Adult smokers who are asthmatics are a group traditionally ignored in randomised controlled trials, for fear of confusion with COPD. There are many studies suggesting that active smoking may cause steroid resistance [33–35]. So could asthmatics who smoke be an attractive group to treat with Montelukast? 44 non-smokers and 39 light smokers age 20–50, with known asthma were randomly assigned to beclomethasone 200 mcg bd or Montelukast 10 mg od for 8 weeks. The groups were well matched at baseline for lung function, airway inflammation measured using induced sputum, and BHR [36]. The primary endpoint was change in prebronchodilator FEV1, secondary outcomes were morning and evening peak expiratory flow rate, PC20 methacholine, symptoms, Quality of Life, and sputum cytology, ECP and tryptase. In terms of the primary end-point, there was no improvement in FEV1 in either group with Montelukast, nor in the smoking asthmatics using beclomethasone; the non-smoking asthmatics, as expected, improved their FEV1. The results of the secondary end-points were challenging. Despite the change in FEV1, morning peak flow only improved in the asthmatic smokers who were treated with montelukast. There were no significant changes in either group with either treatment for sputum eosinophils or PC20 methacholine. This study suggests that Montelukast may be of benefit in asthmatics who smoke; however, this needs confirmation.

Are children who are exposed passively to tobacco smoke, an all too common scenario [37], also steroid resistant? The histone deacetylases (HDAC) acts on nuclear chromatin to control gene expression. HDAC2 is a pre-requisite for corticosteroids to switch off activated inflammatory genes. We studied 19 school age children undergoing fibreoptic bronchoscopy for severe, therapy resistant asthma [38], of whom nine were exposed to environmental tobacco smoke. HDAC2 protein and HDAC2 activity were reduced, whereas HDAC1 and total HDAC activity was unchanged. One could speculate that passive smoke exposure may be a determinant of response to Montelukast in children. However, this needs to be tested prospectively; and the best treatment of passive smoking related asthma is not Montelukast, but smoking cessation.

In summary, we do not have biomarkers to predict the response to Montelukast. The suggestion is that the responders to ICS may be more atopic, and have more eosinophilic inflammation than non-responders. Whether this corresponds to the so-called TH2–hi [39] group in adults remains to be seen. Although this finding raises interesting possibilities for research, currently inflammation and airway reactivity to predict response to therapy in the individual child is not clinically useful.

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**Text Box.** Three step protocol for prophylactic treatment of pre-school wheeze

- **Step 1:** commence montelukast 4.5 mg (depending on age) once daily
- **Step 2:** Discontinue after 6-8 weeks
  - If still symptomatic, further treatment futile
  - If symptom free, could be either therapeutic success, or natural history of the condition
- **Step 3:** Only re-start montelukast if symptoms recur after step 2
SUMMARY AND CONCLUSIONS
Leukotriene receptor antagonists are an exciting novel class of agents from an academic perspective, but at best it is clear they are beneficial for a small minority of pre-school wheezers and school age asthmatics. It is also clear they are prescribed to far more people than actually benefit. We need robust and clinically applicable biomarkers of response to Montelukast; one approach would be to select patients who are dramatic responders to leukotriene receptor antagonists and a group of total non-responders, and compare their genetics in minute detail, including SNPs and gene transcription protocols. Pending such biomarkers, we are compelled to do N of 1 clinical trials, which would be greatly facilitated by having placebos, so that neither paediatrician nor family would know whether active or placebo was being administered. Above all, it is essentially critical to assess response to these agents, and prevent children being left on leukotriene receptor antagonists by default.

FUTURE RESEARCH DIRECTIONS
• Better genetic characterisation of children who respond well to montelukast in comparison to those children who don’t.
• The development and validation of accurate and reliable biomarkers of asthma control in children.

References