Should we use montelukast in wheezy children?

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THE SCALE OF THE PROBLEM

Children who wheeze represent a major public health issue and an ongoing clinical challenge in paediatrics. Around a third of all preschool children experience at least one episode of wheeze and 10% of school-aged children in the UK are prescribed asthma medication. Pertinently, difficult to control or severe asthma in individual children is still associated with substantial morbidity and sometimes preventable mortality on an unacceptable number of occasions in well-developed healthcare systems.

It is imperative that we manage children in the most effective way possible. In the broadest sense, this starts with the accurate diagnosis of wheeze, something in itself demonstrated to be not as straightforward as perhaps we would like to imagine. Then optimal treatment and educational strategies are required to prevent or minimise the severity of future episodes. Accurate phenotyping is necessary to determine the best treatment strategy as the causes and pathogenic mechanisms of wheezing in children are multifactorial. So, where does montelukast fit in to this model of care that we aspire to deliver?

SCIENTIFIC RATIONALE FOR THE USE OF MONTELUKAST AND POSSIBLE ADVERSE EFFECTS

Most would agree that the science underpinning leukotriene receptor antagonists (LTRAs) is intuitively sound. LTRAs block cysteinyl leukotriene receptors that are expressed on the surface of a range of effector cells known to be pivotal in the pathophysiology of wheeze. Leukotrienes are proinflammatory lipid mediators, principally released by mast cells, which trigger bronchoconstriction, eosinophil chemotaxis and mucus secretion in the airway. LTRAs are free of many of the adverse effects associated with (oral) corticosteroids in children. A daily tablet that may be chewable is also attractive to many families. It is important to note, however, that behaviour change is well recognised, which may be significant, along with very rare reports of Churg-Strauss syndrome.

CLINICAL USE OF MONTELUKAST AND THE CONCEPT OF DIFFERENT PHENOTYPES IN CHILDREN WHO WHEEZE

The translation of science from bench to bedside has not been completely straightforward however. The initial theoretical promise of LTRAs in children who wheeze has not been fulfilled and in 'real life' terms, although some individual children experience clear benefit, treatment response in the majority often appears modest at best. However, paediatric asthma guidelines are unanimous in their inclusion of LTRAs. At risk of oversimplification, guidelines draw a distinction between preschool children and those over 5; in addition, most clinicians recognise the broad phenotypes of younger children who only wheeze in association with viral respiratory tract infections, so-called episodic viral wheeze (EVW), and children with atopy and multiple-trigger wheeze (MTW) who tend to be older.

Current BTS/SIGN guidelines for preschool children advise that LTRAs be used as first-line add-on preventer therapy after low-dose inhaled corticosteroids (ICS) or as alternative monotherapy where ICS are not tolerated.[1] However, the distinction between EVW and MTW management is not entirely clear in recent practice recommendations. For children over 5, LTRA use is recommended as second-line add-on therapy where control is inadequate despite combined treatment with a long-acting beta-2 agonist (LABA) and higher-dose ICS—a point where specialist referral may be required.[1]

In preschool children with EVW, montelukast has been evaluated in randomised controlled trials (RCTs) both as maintenance (preventer) and episodic (symptomatic) treatment. Individual RCTs varied in methodology, but in summary some subtle clinical benefit has been demonstrated from episodic montelukast use with reduction in health resource utilisation by around a third (OR 0.65, 95% CI 0.47 to 0.89) compared with placebo[2] and of reduced severity in symptoms[3] (respiratory distress and disruption of activity), again by about a third.[2 3] As maintenance therapy, the PREvention of Viral Induced Asthma study found a statistically significant reduction in exacerbation rates, by around a third (1.60 vs 2.34 episodes/year).[4] In another large RCT maintenance montelukast was not associated with a reduced number of acute episodes, however, there was a slight reduction in symptom scores.[5] A Cochrane review did not find evidence to support maintenance or episodic montelukast in children with EVW for the primary review outcome of reduction in requirement for rescue oral corticosteroids.[6]

Most recently, the WAIT trial randomised 1358 preschool children with two or more previous episodes to receive montelukast or placebo at the onset of wheeze.[7] Findings for the primary outcome of unscheduled medical attendances for wheeze were negative. However, in a predefined subgroup of children with a 5/5 polymorphism in the *ALOX5* promoter gene, which is involved in arachidonic acid metabolism, there was some benefit demonstrated (2.00 vs 2.4 unscheduled attendances/year; IRR 0.80, 95% CI 0.68 to 0.95, p=0.01).[7]

Montelukast has also been studied in young children after respiratory syncytial virus bronchiolitis. A large RCT found no difference in respiratory symptoms, including wheeze, in the montelukast group versus placebo.[8]

Although studies are limited in preschool children with MTW, an RCT of 689 children comparing montelukast to placebo showed statistically significant, but arguably clinically modest, improvements in symptom scores by day and night, requirement for bronchodilators and oral corticosteroids and symptom-free days.[9] Smaller studies have also shown reductions in bronchoconstrictive response to cold-triggered symptoms and airway hyper-responsiveness following montelukast. It is important to note, however, that there is clear evidence for superior efficacy of ICS over LTRAs as monotherapy for children with MTW confirming their respective positions in guidelines.[10]

In terms of LTRAs as add-on therapy in children evidence is limited, partly due

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to a shortage of good quality studies. A Cochrane review including four studies involving children aged 6–18 years found no significant difference in exacerbation rates between ICS and LTRA combination treatment and ICS alone at the same or increased dose.[11] The Best Add-on Therapy Giving Effective Responses trial randomised children aged 6–17 years with poorly controlled asthma on fluticasone 200 mcg/day to receive add-on treatment in varying sequence in the form of a LABA (salmeterol), montelukast or increased fluticasone dose.[12] A beneficial response to salmeterol was most likely compared with montelukast (relative probability 1.6, 95% CI 1.1 to 2.3, p=0.004) or increased ICS dose (relative probability 1.7, 95% CI 1.2 to 2.4, p=0.005).[12] Importantly, there was variation in response and some individual children responded best to LTRA or increased ICS dose.

IN PURSUIT OF PRECISION MEDICINE, A PRAGMATIC WAY FORWARD

One explanation for the varied results of studies discussed above is the increasingly recognised complex and dynamic heterogeneity of different endotypes in children who wheeze. This concept resonates with experiences of healthcare professionals who frequently manage children who wheeze and observe varying treatment responses and individual trajectories over time and with those who wrestle with the careful design of studies to objectively measure the efficacy of therapeutic interventions or who study the complex inter-related pathways and mechanisms involved in the pathophysiology of airway disease.

A major challenge is to successfully identify practical biomarkers or other tools to accurately, cost-effectively and rapidly select the right treatment for an individual child at the right time. Arguably, the *ALOX5* polymorphism subgroup in the WAIT study may provide a glimpse of this but genome sequencing is not yet a practical option at the clinical coal-face. In the absence of these key tools for precision medicine, the most appropriate way forward for the thoughtful clinician is to perform an 'n of 1' therapeutic trial in an individual patient to assess potential benefit from montelukast. Such a trial should be as objective as possible and finite in length remembering the variable natural history of children who wheeze. Undoubtedly, a significant minority of children will benefit from montelukast and this approach would appear the most effective way to identify such children, while minimising needless overprescription to children who do not benefit.

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