Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate 5-lipoxygenase (*ALOX5*) promoter genotype: a multicentre, randomised, placebo-controlled trial

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Scientific summary

Oral montelukast therapy for preschool wheeze

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Scientific summary

Background

Wheeze in preschool children is a common and important cause of morbidity, with an associated social and economic burden through strain on health services and parental resources. Current evidence does not support the use of oral corticosteroids in this population because of a lack of efficacy in reducing hospital stay and demonstrable oral treatment-associated morbidity when used to excess. The majority of children wheeze only with colds, with few or no symptoms in the interim. There is a need for a treatment that can be administered effectively during symptomatic episodes but can be discontinued when children are well.

The cysteinyl leukotrienes (cLTs) are inflammatory mediators derived from arachidonic acid that have potent bronchodilator effects. Previous work has shown a transient increase in leukotriene (LT) production [measured as urinary leukotriene E4 (LTE_4)] in preschool children during acute wheezing episodes, implicating them as the transient mediator for episodic viral wheeze in this population.

Montelukast (Singulair®, Merck Sharp & Dohme Ltd) is the only LT receptor antagonist licensed for use in children. It is a competitive inhibitor of the cLT receptor binding site and prevents the downstream bronchoconstrictor and pro-inflammatory effects of the cLTs. Moreover, it is safe and orally available, with an appropriate half-life and posology suitable for all ages. Previous work has suggested a role for intermittent therapy in the management of acute childhood wheeze, but the effects have been modest. Analysis of adult trials suggests that variation in copy number of a guanine–cytosine-rich specific protein 1-binding motif (the wild type has five copies) in the promoter region of the arachidonate 5-lipoxygenase (*ALOX5*) gene may influence response to montelukast, presumably by altering baseline or exacerbation-related LT production.

Primary objectives

1. To assess the efficacy of parent-initiated intermittent montelukast for the reduction of unscheduled medical attendances for preschool wheeze.
2. To explore the role of the *ALOX5* promoter genotype in montelukast efficacy.

Secondary objectives

1. To assess the impact of intermittent montelukast on respiratory morbidity.
2. To assess the impact of montelukast on health service usage.
3. To assess the impact of intermittent montelukast on adverse events (AEs).
4. To assess the impact of intermittent montelukast on concomitant medication use.
5. To gather exploratory data on related LT pathway genes.
6. To gather exploratory data on urinary LT/eicosanoid output.
7. To assess impact of intermittent montelukast on economic outcomes.
8. To assess qualitative outcomes related to parent-initiated intermittent therapy for preschool wheeze and participation in a genetically stratified interventional trial.

Methods

Overall, it was hypothesised that montelukast would be moderately effective but that a subgroup of children with a variant (non-5 repeat) allele on one or both chromosomes would have a greater response to montelukast, manifesting as a decreased need for unscheduled medical attention compared with their peers when treated with montelukast.

To test this hypothesis we recruited children from primary and secondary care settings. Eligible children were aged 10 months to 5 years, had had two or more previous episodes of wheeze, with one occurring within the previous 3 months, and had no associated significant respiratory morbidity. Younger and older children were excluded so as not to confuse the pathology studied with viral bronchiolitis or classical asthma. At enrolment, children provided salivary deoxyribonucleic acid and were stratified by *ALOX5* genotype, with one stratum comprising those with five copies of the *ALOX5* promoter on each allele and the other comprising all those with one or more non-5 repeat allele. The two strata were subsequently independently randomised in a 1 : 1 ratio (randomly permuted blocks of 10) to receive montelukast oral granules or identical placebo every day for 10 days from the start of a cold or wheezing episode. Need for unscheduled medical attention over a period of 12 months was assessed as the primary outcome. Outcome data were collected via a treatment diary completed with every course of investigational medicinal product and via a bimonthly investigator telephone call which additionally screened for AEs.

We also measured urinary LTE_4 at baseline and during exacerbation (where possible) to provide pathophysiological corroboration of any associations observed. Urine was collected fresh into a universal container and placed on ice before being transferred within 48 hours to a freezer at –70 °C. Urine samples were then batch analysed using high-performance liquid chromatography–tandem mass spectrometry for a number of eicosanoid mediators, with results indexed to urinary creatinine.

A subset of recruits underwent semistructured qualitative interviews conducted by an experienced qualitative researcher, with an interpreter where required. Questions addressed background information about the child and family, as well as parental experiences and attitudes to their role in the trial. Interviews were audio-recorded, transcribed and imported into Nvivo9™ (QSR International, Pty Ltd, VIC, Australia; a qualitative data analysis program) for analysis.

Results

Out of the 1358 subjects recruited, data on which to assess the primary outcome were available for 1308 (96%) subjects. Analysis was by intention to treat. Overall, montelukast did not outperform placebo in intermittent usage for preschool wheeze [incidence rate ratio (IRR) = 0.88; $p = 0.06$]. In children treated with montelukast, use of rescue oral corticosteroids, a recognised marker of severity, was marginally reduced (IRR 0.75; $p = 0.03$); however, the study was not adequately powered to robustly detect such a change.

Analysis by genotype suggested an improved montelukast effect (contrary to our hypothesis, but in keeping with certain earlier work) in the wild-type (5/5) stratum (IRR = 0.80; $p = 0.01$). When subject to more detailed scrutiny this observation was not statistically robust, with a *p*-value for interaction of only 0.08. No effect was seen when the primary outcome was analysed by use of inhaled corticosteroids, wheezing phenotype or alternative genotype grouping x/x versus [x/5 + 5/5].

Urinary eicosanoid results

Leukotriene E_4 appeared higher in subjects with two variant alleles (x/x) ($p < 0.05$). This was inconsistent with the direction of association predicted by the possible improved montelukast effect in the 5/5 population. Analysis of urinary cotinine and urinary LTE_4 by LT pathway single nucleotide polymorphisms (SNPs), etc., remains ongoing.

Qualitative results

Bangladeshi families were relatively reluctant to participate in the qualitative study, despite strong engagement with the parent study. Anxiety related to wheezing was a common primary motive for trial enrolment. Parents viewed the trial as a route to improved treatment. Verbal delivery of trial information appeared to be more effective than study literature, especially for Bangladeshi families, with low parental literacy and high levels of trust in medical professionals potential contributors to this effect. All ethnic groups expressed a low understanding and/or retention of essential study concepts such as randomisation and genetic testing.

Conclusions

This study does not support the routine use of intermittent montelukast in preschool wheezing children. It does not speak to the value of continuous montelukast in this population; neither does it preclude the consideration of short-term therapeutic trials on an individual patient basis in this context. The suggested superior montelukast response in the 5/5 stratum is of interest but is not robust insofar as the test of interaction does not meet statistical significance and the finding contradicts both the a priori hypothesis and the urinary LTE_4 data.

Future research

The effect seen in the 5/5 stratum will be prospectively evaluated in a study population comprising children with only wild-type (5/5) alleles. Should this study be negative it remains possible that a montelukast-responsive subgroup exists. In the course of this trial we have collected data on more than 100 LT pathway SNPs with associated urinary eicosanoid profiles and demographic data. Subsequent work will interrogate this data set for candidate genes and biomarkers that might identify any responsive subgroup with a view to hypothesis generation for future large-scale trials of stratified therapy in preschool wheeze.

Trial registration

This study is registered as ClinicalTrials.gov NCT01142505.

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