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| Project Title: | Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate-5-lipoxygenase (ALOX5) promoter genotype. |
| Project Ref: | 08-43-03 |
| Cost: | £1,794,050 |
| Lead Applicant & Institution: | Professor Jonathan Grigg Centre for Paediatrics Barts and the London School of Medicine and Dentistry |
| Start Date: | 1 November 2009 |
| Plain English Summary: | <p>A quarter of all UK children will have at least one attack of wheeze during the preschool period (1 to 5 years of age). Severe attacks of wheeze in these young children are usually triggered by viral-colds. The majority of affected children will only wheeze with colds, although these attacks may be severe and repeated resulting in GP attendances and hospital admissions. This pattern of wheeze is called "episodic" preschool wheeze.</p> <p>A minority of preschool children wheeze both with and between colds - a pattern that is called "multi-trigger" preschool wheeze. In real life this distinction is blurred, with preschool children changing their pattern of wheeze over time. What is clear is that asthma therapies that are effective in older children with classical "allergic" asthma may not necessarily be effective in preschool wheeze. For example, although a short-course of oral steroids is very effective in treating attacks of wheeze in school age children with "allergic" asthma, we have shown in 2 major trials that a short course of oral steroids does not reduce the severity of attacks of preschool wheeze.</p> <p>Recently, montelukast, an oral medicine that blocks a substance (leukotriene) that narrows the breathing tubes, has shown promise in preschool wheeze. However, to date, only modest benefits have been reported when large groups of children have been studied. One explanation for this, is that a significant proportion of preschool children do not respond to montelukast, but there is a subgroup who are genetically programmed to respond very well. Recent analysis of trials of montelukast suggests that this responsive subgroup may be defined by variations in leukotriene-producing genes. Thus an understanding of the role of leukotriene genes and leukotriene production in preschool wheeze may better target montelukast treatment in this age group, and inform the development of new therapies.</p> <p>The clinical aim of this trial is to assess whether intermittent montelukast is an effective treatment strategy in preschool wheeze. The mechanisms aim of the trial is to determine whether there is a genetically highly-responsive subgroup of children. In designing this trial we have incorporated several</p> |

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| | <p>novel aspects.</p> <p>First, parents will be able to adjust the use of oral montelukast to their child's symptoms. This allows us to recruit both "episodic" and "multi trigger" patterns of preschool wheeze - and control for any change in wheeze pattern during the trial. Second, before we issue the trial medication, we will assess children's leukotriene genes, focusing primarily on a gene called ALOX5. This ALOX5 "stratification" step will ensure that an equal number of potentially "treatment-responsive" children receive the active drug (montelukast) and the dummy medicine - and the equal numbers will help us to assess the role of ALOX5. For the trial, we will first recruit 1,300 children with a history of preschool wheeze, then divide them into the group with "responsive" and "less responsive" genes by their ALOX5 status. We will then issue parents with the trial medication; 50% will be given montelukast and 50% will be given dummy medication. Parents will start the trial medication whenever their child develops a cold, and stop the medication when wheeze resolve. Parents will also be able to give the trial medication for wheeze between colds. Over the 12 month trial period, we will assess the number of unscheduled attendances to a medical practitioner for wheeze for each child. At the end of the trial, we will determine whether montelukast is effective then whether there is a difference in response to montelukast between the 2 ALOX5 gene groups.</p> <p>At the same time, we will measure many other genes that may influence response to montelukast, as well as the amount of leukotrienes that are excreted in the urine before and during attacks. Using these results, we will be able to both inform national treatment policy, and develop new concepts on the mechanism of preschool wheeze that will inform the development of new therapies. Since children will continue to receive "normal" inhaled therapy, there are no ethical issues in giving a dummy medicine to half of the 1,300 children to be recruited. The study will be the largest trial in wheezy preschool children to date, and may open up genetic testing in preschool wheeze.</p> |
| <p>Abstract:</p> | <p><u>Design.</u> An independent, 12 month, multicentre, parallel group, double-blind, randomised placebo-controlled trial.</p> <p><u>Settings.</u> Recruitment will be based in at 40 GP practices in the East London GP Academic Network, at 60 practices in the Norwich Academic Primary Care Network, the Accident and Emergency Department and paediatric wards of the Barts and the London Children's Hospital, and the A&E and paediatric wards of the University Hospitals of Leicester NHS Trust Children's Hospital.</p> <p><u>Intervention being evaluated.</u> The trial will test the hypothesis that intermittent treatment with montelukast is efficacious in preschool wheeze, and that there is a highly responsive subgroup of children defined by a variant number [x/x or 5/x (where x is not equal to 5)] of SP1 repeats of the membrane-bound arachidonate-5-lipoxygenase gene (ALOX5).</p> <p><u>Measurement of outcomes and duration of follow up.</u> The primary clinical outcome is the number of attacks of wheeze over the 12 month trial period requiring an unscheduled medical opinion. An attack is defined as clinician-diagnosed attack of wheeze, requiring an unscheduled attendance to either a general practitioner, or to an accident and emergency department. The secondary outcomes are; i) number of days of wheeze over the 12 month trial period, ii) number of admissions to hospital > 4 hrs duration, iii) time to first attack of wheeze, iv) parent assessment of efficacy of trial medication, v) need for additional asthma</p> |

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| | <p>therapy (regular inhaled steroids, and long acting beta 2 agonists), and vi) change in weight of salbutamol metered dose inhaler canister. In addition to assessing the effect of ALOX5 status on the primary outcome, children will be genotyped for 150 single nucleotide polymorphisms (SNPs) associated with the leukotriene (LT) pathway, and will have baseline and exacerbation urinary cysteinyl leukotrienes assessed. Children will be followed up for 12 months. Parents' views on the intervention will be assessed in a qualitative study.</p> <p><u>Sample size</u> 1,050 children in total.</p> |
| ISRCTN: (if applicable) | 01142505 |
| Project Protocol: | www.eme.ac.uk/projectfiles/084303protocol.pdf |
| Project website: (if applicable) | http://www.ihse.qmul.ac.uk/chs/pctu/current_projects/wait/25693.html |
| URL of this Page: | www.eme.ac.uk/projectfiles/084303info.pdf |