

RESEARCH AND DEVELOPMENT DEPARTMENT

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RE: MASCOT results available in EuDRACt

Please find the below supplementary information in addition to the following Executive Summary pertaining to this trial.

<u>Study Title:</u>	<u>Management of Asthma in School Age Children on Therapy</u>
<u>Chief Investigator:</u>	<u>Professor Warren Lenney</u>
<u>Co-Sponsors:</u>	University Hospitals of North Midlands NHS trust (previously the University Hospitals of North Staffordshire NHS Trust), Keele University
EudraCT:	2008-000511-16
REC:	08/H1010/8 NRES: North West REC
Name of IMP	Fluticasone propionate Salmeterol montelukast Run in period (all participants): Fluticasone propionate inhaler 200 micrograms / day for 4 weeks Randomised to 1 of 3 treatment arms: A: Inhaled fluticasone propionate 100 micrograms twice daily plus placebo tablet once daily

	<p>B: Inhaled fluticasone propionate 100 micrograms and salmeterol 50 micrograms twice daily (combination inhaler) plus placebo tablet once daily</p> <p>C: Inhaled fluticasone propionate 100 micrograms twice daily plus montelukast 5mg tablet once daily</p>
Number of Sites	<p>13 Secondary Care sites:</p> <p>University Hospital of North Staffordshire, Prof warren Lenney)</p> <p>Royal Devon and Exeter NHS Foundation Trust (Dr Andrew Collinson , Dr Patrick Oades)</p> <p>Arrowe Park Hospital, Wirral (Dr David Lacy)</p> <p>Leicester Royal Infirmary (Dr Hitesh Pandya)</p> <p>Norfolk and Norwich University Hospitals (Dr Chris Upton)</p> <p>Bristol Royal Hospital for Children (Dr Tom Hilliard)</p> <p>Royal London Hospital (Dr Caroline Pao)</p> <p>Derbyshire Children's hospital (Dr Will Carroll)</p> <p>Queens Medical centre Nottingham (Prof Harish Vyas)</p> <p>Alder Hey Children's NHS foundation Trust (Dr Jon Couriel)</p> <p>Royal Manchester Children's Hospital (Dr Clare Murray)</p>

	<p>Royal Aberdeen Children's hospital (Dr Stephen Turner)</p> <p>University Hospitals Coventry and Warwickshire NHS Trust (Dr Edward Simmonds)</p>
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Dr Darren Clement
R&D Manager

Executive summary

Background

Asthma affects one in eight children nationwide, the majority of whom are prescribed low-dose inhaled corticosteroids (ICSs). When treatment with low-dose ICSs fails to control asthma symptoms or adequately prevent exacerbations, national guidelines of the British Thoracic Society and the Scottish Intercollegiate Guidelines Networks suggest ensuring compliance, maximising inhaler technique and treating comorbidities such as rhinitis. If asthma remains uncontrolled, the guidelines recommend increasing the treatment (step 3 of the national guidelines). The evidence base at step 3 of the guidelines is much more limited for children than for adults. Few studies have been undertaken in children and most that have taken place have used inappropriate adult-based outcomes such as lung function measurements, which suffer from assay insensitivity and fail to capture the episodic nature of much of childhood asthma. Pharmaceutical company studies, conducted to obtain a licence for a medicinal product, have generally been of short duration and have not added to clinicians' understanding of how and where to use the medications. In addition, they have not necessarily selected a representative population because of their tight entry criteria and their intensive study requirements.

Management of Asthma in School age Children On Therapy (MASCOT) was designed to address the need for a simple, pragmatic (but placebo-controlled and double-blind) trial with outcomes that would be of practical benefit to children and would provide evidence for the use of add-on medications in the most cost-effective and efficient way. Since MASCOT was commenced the Best Add-on Therapy Giving Effective Response (BADGER) trial has been completed and published, concluding that 100 µg of fluticasone [Flixotide®, GlaxoSmithKline (GSK)] plus 50 µg of a long-acting beta-2 agonist twice daily (long-acting beta-2 agonist step-up) (Serevent®, GSK) was significantly more likely to provide a better response than either 250 µg of fluticasone twice daily (ICS step-up) or 100 µg of fluticasone twice daily plus 5 or 10 mg of a leukotriene receptor antagonist daily (leukotriene receptor antagonist step-up) (Singulair®, Merck Sharp & Dohme). This study, however, required reversibility or hyper-responsiveness as an entry criterion, which excluded many patients, was short term in nature and focused primarily on symptomatic control as measured by the Childhood Asthma Control Test as opposed to exacerbations.

Objectives

The main research objective was to determine whether or not, in children aged 6–14 years with asthma that is uncontrolled on low-dose ICSs, their control could be improved by adding in a long-acting beta-2 agonist (salmeterol, Seretide®, GSK) or a leukotriene receptor antagonist (montelukast, Singulair) as measured by a reduced number of exacerbations requiring treatment with oral corticosteroids over the 48-week study period. Secondary objectives were to assess differences between treatment groups in terms of quality of life, as measured by the Paediatric Asthma Quality of Life Questionnaire with Standardised Activities [(PAQLQ(S)) and the Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ); time from randomisation to first exacerbation requiring treatment with a short course of oral corticosteroids; number of school days missed due to respiratory problems; number of hospital admissions due to respiratory problems; amount of rescue beta-2 agonist therapy prescribed; time from randomisation to treatment withdrawal (due to lack of efficacy or side effects); lung function at 48 weeks (as assessed by spirometry); cost-effectiveness; and adverse events.

Methods

Population

Children were aged between 6 and 14 years with uncontrolled asthma following inhaler technique guidance. This group reflected the typical children who were prescribed step-up treatments according to UK asthma guidelines.

Setting

Children were recruited from primary and secondary care in the participating sites throughout England and Scotland. The main strategies for identifying eligible patients were from secondary care referrals (outpatients and inpatients) and from general practice database searches. The searches were followed by one mail-out inviting participation in the study. As recruitment proved difficult, further strategies were developed during the study. The trial co-ordinator and chief investigator visited all participating sites to discuss and develop new concepts for improving recruitment. These included planned second mail-outs at 1 month if there had been no response, or encouragement of telephone calls from the primary care staff to their patients at home. Two centres wanted to involve local community pharmacists in offering literature about the study, giving details of the research team's email address or telephone numbers. One centre agreed to develop computer pop-up reminders for general practitioners when any potentially eligible patient was seen in the surgery. Other centres wanted reminders posted in surgery waiting rooms encouraging families to ask about suitable studies that were under way. Similar views applied to secondary care outpatient clinic facilities. It became clear that sites with clear effective working practices between the Medicines for Children Research Network (MCRN), Primary Care Research Network (PCRN) and Comprehensive Local Research Network (CLRN) recruited the most patients. Another body of help could have been harnessed through the school nursing service.

Screening

Children were screened to assess eligibility at T-4 (T-4 represented the start of the 4-week run-in period, 4 weeks later being T0 or time zero) based on the following criteria:

Inclusion criteria (T-4)

1. Children with physician-diagnosed asthma aged from 6 years to 14 years 11 months.
2. Children who required frequent short-acting beta-2 agonist relief therapy: seven or more puffs in the past 7 days.
3. Children with symptoms of asthma (i.e. wheeze, shortness of breath but not cough alone) that resulted in:
 - i. nocturnal waking in the last week and/or
 - ii. interference with usual activities in the last week and/or
 - iii. those who had had exacerbations, defined as a short course of oral corticosteroids, an unscheduled general practitioner or accident and emergency (A&E) department visit or a hospital admission within the past 6 months.
4. Fully informed written (proxy) consent and assent, where appropriate.

Exclusion criteria (T-4)

1. Children who received long-acting beta-2 agonists, leukotriene receptor antagonists, regular theophylline therapy or high-dose ICSs ($>1000\mu\text{g}$) and unlicensed beclometasone dipropionate or equivalent (at the discretion of the investigator).
2. Children with other respiratory diseases, cystic fibrosis, cardiac disease or immunological disorders.

Eligible children who were able to give informed consent entered a 4-week run-in period in which expert inhaler technique training was given by the research nurse along with a prescription for fluticasone propionate inhaler ($100\mu\text{g}$ twice daily). Children were invited to attend a further eligibility assessment at T0. Those who then met the following criteria were randomised and followed for a further 48 weeks (T0-T48).

Inclusion criteria (T0)

1. Children with asthma aged from 6 years to 14 years 11 months.
2. Children who required frequent short-acting beta-2 agonist relief therapy: seven or more puffs in the past 7 days.
3. Children with symptoms of asthma (i.e. wheeze, shortness of breath but not cough alone) resulting in:
 - i. nocturnal waking in the last week and/or
 - ii. interference with usual activities in the last week.
4. Continuing consent/assent (where appropriate).

Exclusion criteria (T0)

1. Children whose asthma was controlled after the 4 week run-in, in which control was defined as the absence of any symptoms of asthma (except cough alone) or when the symptoms of asthma had not interfered with usual activities in the last week.
2. Children who were receiving long-acting beta-2 agonists, leukotriene receptor antagonists, regular theophylline therapy or high-dose ICSs ($> 1000\mu\text{g}$) and unlicensed beclometasone dipropionate or equivalent (at the discretion of the investigator).
3. Children with other respiratory diseases, cystic fibrosis, cardiac disease or immunological disorders.

Interventions

During the 4-week run-in period all patients were commenced on fluticasone propionate inhalers at $200\mu\text{g}$ per day ($100\mu\text{g}$ twice daily). Children who remained symptomatic at the end of the run-in period were randomised into one of three double-blinded treatment regimens:

- A inhaled fluticasone propionate $100\mu\text{g}$ twice daily plus placebo tablet once daily
- B inhaled fluticasone propionate $100\mu\text{g}$ and salmeterol $50\mu\text{g}$ twice daily (combination inhaler) plus placebo tablet once daily
- C inhaled fluticasone propionate $100\mu\text{g}$ twice daily plus montelukast 5-mg tablet once daily.

Results

The first patient was registered on 27 January 2009 with the first patient randomised on 19 May 2009. Recruitment rates were poor throughout the trial and a funding extension application was rejected by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, which resulted in the trial being closed prematurely on 24 June 2010. Thirteen centres registered at least one patient and 12 centres randomised at least one patient. A total of 898 children were screened to enter the trial, 166 were registered at T-4, 63 were randomised at T0 and 38 completed a 48-week follow-up and could provide data for the primary analysis.

None of the results was statistically significant. At 48 weeks, the rate ratio (RR) of exacerbations requiring treatment with oral corticosteroids was 0.91 [98.3% confidence interval (CI) 0.07 to 12.05, $p = 0.93$] for fluticasone compared with fluticasone plus salmeterol; 1.10 (98.3% CI 0.06 to 18.6, $p = 0.94$) for fluticasone compared with fluticasone plus montelukast; and 1.21 (98.3% CI 0.09 to 15.97, $p = 0.86$) for fluticasone plus salmeterol compared with fluticasone plus montelukast. These results were based on only 38 patients, seven of whom had at least one exacerbation. The CIs are extremely wide and included clinically important RRs that could favour any of the treatments. Although 54 patients could be included in the 24-week analysis, results were similarly inconclusive with RRs of 1.93 (98.3% CI 0.35 to 10.67, $p = 0.36$) for fluticasone compared with fluticasone plus salmeterol; 2.84 (98.3% CI 0.43 to 18.79, $p = 0.19$) for fluticasone compared with fluticasone plus montelukast; and 1.47 (98.3% CI 0.17 to 12.39, $p = 0.67$) for fluticasone plus salmeterol compared with fluticasone plus montelukast. Analysis of time to first exacerbation was also inconclusive (overall log-rank test $p = 0.39$) with hazard ratios (HRs) of 0.63 (95% CI 0.19 to 2.08) for fluticasone compared with fluticasone plus salmeterol; 1.52 (95% CI 0.34 to 6.7)

for fluticasone compared with fluticasone plus montelukast; and 2.37 (95% CI 0.68 to 8.2) for fluticasone plus salmeterol compared with fluticasone plus montelukast.

The mean quality of life score had improved at 24 and 48 weeks for all treatment groups across all domains, both for the child and for the caregiver; however, there were no statistically significant differences in mean scores adjusted for baseline values for any of the pair-wise treatment comparisons. Fewer children missed at least one day of school over 48 weeks on fluticasone plus montelukast (18.2%) than on fluticasone (63.6%) and fluticasone plus salmeterol (60%), and more children on fluticasone plus salmeterol (71.4%) required at least one beta-2 agonist than children on fluticasone (54.5%) or fluticasone plus montelukast (58.3%) over 48 weeks. However, these patterns were not supported by the 24-week data. The wide CIs for pair-wise comparisons of relative treatment effects include clinically important differences that could favour any of the treatments. Only a few children required a hospital admission during the trial, with relative treatment effects difficult to estimate.

Adverse events were mild or moderate and were similar across treatment groups except that more patients reported nervous system disorders on fluticasone plus montelukast [seven patients (33.3%)] than on fluticasone plus salmeterol [one patient (4.3%)] and fluticasone [five patients (26.3%)]. There were seven mild or moderate serious adverse events that were unrelated to treatment and no suspected unexpected serious adverse reactions were reported.

Care is needed when interpreting the limited data available for a subset of 62 children who were registered but not randomised. The results suggest that their regimen was not entirely successful in spite of the control achieved over the 4-week run-in. In the following 12 months 14.5% had an exacerbation, 80.6% required at least one beta-2 agonist prescription and 29% required a prescription for at least one further asthma treatment.

Conclusions

Because of poor recruitment and the premature closure of the trial, the available data were limited and did not allow us to make specific conclusions. This is the major weakness of the study. We have, however, identified different ways of addressing recruitment in primary and in secondary care, which may be helpful to other researchers in the future.

Implications for health care

The question of how best to treat children uncontrolled on ICSs is mainly unanswered. Since the commencement of the MASCOT study an American asthma study has been published which concluded that LABA step-up was more likely to provide a better response than either fluticasone alone or fluticasone plus montelukast (the BADGER trial). This is in keeping with the national UK asthma management guidelines. The BADGER study, however, suffered from major limitations: (1) inclusion required reversibility in spite of taking ICS treatment, that is, the recruits were not representative of typical asthma patients in the community; (2) the study length was only 16 weeks; and (3) the end point was symptom based. All therapy options showed improvement but the likelihood of success was greater in the LABA group. Another study compared inhaled fluticasone 100µg twice daily with inhaled fluticasone 200µg twice daily or a fluticasone/salmeterol combination (Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Strater C, Steinkamp G, *et al.* Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). *Pediatric Pulmonol* 2009;**44**:1132–42). This study also required reversibility, was of short duration (8 weeks) and was terminated prematurely. The results showed that lung function was better with salmeterol as were days without symptoms.

Recommendations for research

- The MASCOT study identified challenges for recruiting patients with a chronic condition treated mainly in primary care. This warrants further investigation and our new recruitment methods can be considered in future paediatric studies.
- Alternative study designs may be required to answer the key research question of what is the most appropriate treatment for children uncontrolled on low-dose ICSs.

Trial registration

This trial is registered as ISRCTN03556343.

Funding

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