Treatment guided by fractional exhaled nitric oxide in addition to standard care in 6- to 15-year-olds with asthma: the RAACENO RCT

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Scientific summary

The RAACENO RCT

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Scientific summary

Background

Asthma is the most common chronic condition in childhood and affects 1.1 million children in the UK. The two key goals of asthma treatment are to achieve asthma control on a day-to-day basis and to prevent asthma exacerbations. Asthma exacerbations (synonymous with asthma attacks) are a worsening of symptoms; they are usually treated with oral corticosteroids (OCs) and can result in hospitalisation.

Asthma medicines are considered to be relievers (taken on an ad hoc basis to relieve symptoms) or preventers (taken on a daily basis independent of symptoms). There is an extensive evidence base that reports that asthma symptoms can be reduced by preventer treatments, such as inhaled corticosteroids (ICs), inhaled long-acting beta-agonists (LABAs) and oral leukotriene receptor antagonists (LTRAs). The initial asthma preventer treatment for children aged 6–15 years that is recommended by all guidelines is ICs, but there is uncertainty about the best treatment option when symptoms are not controlled by ICs alone.

The concentration of nitric oxide in exhaled breath [called fractional exhaled nitric oxide (FeNO)] is elevated in children with asthma compared with children without asthma. FeNO is considered to be a surrogate for the allergic airway inflammation that is characteristic of childhood asthma. FeNO levels are higher before and during an asthma exacerbation, and fall again after the exacerbation. The role of FeNO in guiding asthma treatment in children is uncertain. Current guidelines do not recommend that FeNO is used to guide asthma treatment in children, but a recent Cochrane review suggests that FeNO-guided asthma management may be useful in reducing asthma exacerbations in children (Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016;**11**:CD011439).

Objectives

The aim of the RAACENO (Reducing Asthma Attacks in Children using Exhaled Nitric Oxide) trial was to compare treatment guided by both symptoms and FeNO with treatment guided by symptoms alone (standard care) in children with asthma who are at risk of an asthma exacerbation, in terms of the presence of any asthma exacerbations over 12 months that required treatment with OCs.

Methods

RAACENO was a pragmatic, multicentre, randomised controlled trial. We recruited children with asthma aged 6–15 years who used ICs and had experienced an exacerbation in the previous 12 months.

Participants were recruited predominantly from asthma clinics in 35 UK hospitals, as well as seven primary care practices. Participants were randomised (using remote web-based 1 : 1 randomisation minimised on recruitment centre, age, sex and British Thoracic Society treatment step) to receive either asthma treatment guided by symptoms plus FeNO (intervention group) or asthma treatment guided by symptoms only (standard-care group). Treatment recommendations were protocolised within a web-based treatment algorithm dependent on symptom control, IC adherence (objectively measured using an electronic logging device), current treatment and, within the intervention group, changes in FeNO. Participants attended assessments at 3, 6, 9 and 12 months post randomisation. At each

follow-up assessment, the web-based algorithm was applied and a treatment recommendation was made. Clinical teams could follow the treatment algorithm or offer an alternative treatment recommendation.

The primary outcome was asthma exacerbation requiring OCs in the 12 months post randomisation, as reported by the families at each follow-up visit. Secondary outcomes included time to first asthma exacerbation, number of asthma exacerbations during follow-up, unscheduled health-care contacts, lung function [per cent predicted (%) forced expiratory volume in 1 second (FEV_1)], FeNO, daily dose of ICs, asthma control and quality of life.

The study included an evaluation of health-care costs, which considered primary and secondary care contacts and asthma treatment. This information was collected at each assessment and was supported by a patient-held diary.

A qualitative process evaluation was also incorporated into the study design to explore experiences and determine the acceptability of the intervention through interviewing a sample of families (parent and child pairs) across both groups of the trial and trial staff.

The trial was registered prospectively (ISRCTN67875351) and received Research Ethics Committee approval, and all participants provided fully informed consent.

Results

A total of 515 participants were recruited between June 2017 and August 2019, from 42 sites. Sixteen participants were recruited in primary care. Six participants were recruited but did not meet the inclusion criteria and were excluded after randomisation.

Baseline characteristics

The two randomised groups were well balanced in terms of demographic and disease characteristics at baseline. The mean age of the participants was 10.7 years and 60.5% were male. The majority of children (61.8%) were a healthy weight. The median number of courses of OC tablets for an asthma exacerbation in the previous year was three, and the median number of admissions to hospital because of asthma in the previous year was one. At baseline, the median daily dose of ICs was 400 µg of budesonide equivalent; 33% of participants received > 800 µg daily. In total, 75.8% of participants were prescribed a LABA and 59.3% were prescribed a LTRA. Using recognised cut-off points from the Asthma Control Test/Children's Asthma Control Test (i.e. score of > 19), asthma was controlled in 50.3% of participants.

The median baseline FeNO measure was 21 parts per billion (ppb). The mean percentage FEV_1 in children was 90%. The proportions of children who were reported to ever have had eczema, rhinitis and food allergy were 57.6%, 59.7% and 27.4%, respectively. The median score for the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) was 5.74.

Clinical findings

The primary outcome (at least one exacerbation treated with OCs in the 12 months following randomisation) was available for 506 participants (255 in the intervention group and 251 in the standard-care group) and they were included in the intention-to-treat analysis.

The primary outcome occurred in 123 out of 255 (48.2%) participants allocated to the intervention group and in 129 out of 251 (51.4%) participants allocated to the standard-care group. In the adjusted model, the odds ratio for the primary outcome was 0.88 [95% confidence interval (CI) 0.61 to 1.27] for participants allocated to the intervention group compared with the standard-care group. This estimate was not statistically significant in any of the predefined subgroups.

In 377 of the 1771 assessments, the local clinical team did not deliver the algorithm's treatment recommendation. In the per-protocol analysis (including those participants considered 'compliant' with the algorithm in at least three of the visits at baseline and 3, 6 and 9 months), 84 out of 165 (50.9%) participants in the intervention group and 79 out of 153 (51.6%) participants in the standard-care group had at least one exacerbation (adjusted odds ratio 0.98, 95% CI 0.61 to 1.55). In a complier-average causal effect analysis, adjusting for compliance with the algorithm recommendations, the odds ratio for the primary outcome was 0.82 (95% CI 0.48 to 1.41).

There was no difference in secondary outcomes (time to first asthma exacerbation, number of asthma exacerbations during follow-up, unscheduled health-care contacts, lung function, FeNO, daily dose of ICs, asthma control or quality of life) between the intervention and the standard-care groups. Over the course of the trial, participants in both groups had clinically meaningful improvements in asthma control and quality-of-life scores.

In both treatment groups over the 12 months of follow-up, there were improvements in asthma control and PAQLQ scores that exceeded the minimum clinically important difference.

There were no serious adverse events or deaths among participants.

At each time point (baseline and 3-, 6- and 9-month follow-up), between 20% and 24% of treatment recommendations made by the algorithm were not followed. There was little difference between the groups in the proportions of recommendations not followed. Where the treatment recommendation was 'remain the same', compliance with the treatment recommendation was much more common than if the recommendation was to step up or step down treatment. The majority of reasons for non-compliance with the treatment algorithm were based on beliefs, most frequently that no step up or step down in treatment was required.

Health economics

The economic evaluation compared treatment guided by FeNO plus symptoms (intervention group) with treatment guided by symptoms alone (standard-care group) in terms of asthma-related NHS costs, the number of asthma exacerbations and total quality-adjusted life-years (QALYs) over a 12-month follow-up period. Costs falling directly on patients and indirect costs associated with time lost from productive activities were also considered in a separate analysis.

The mean prescribed preventative treatment costs (including the cost of inhalers, LTRA and other preventative treatments) were £718.16 (95% CI £525.70 to £910.63) and £732.71 (95% CI £502.03 to £963.40) for the standard-care group and intervention group, respectively. When these treatment costs were adjusted for adherence to the prescribed treatment, they fell to £556.96 (95% CI £376.39 to £738.54) and £561.73 (95% CI £345.12 to £778.34) for the standard-care group and intervention group, respectively. Resource use reported to be associated with exacerbations translated into a mean cost per exacerbation of £291.32 (95% CI £207.07 to £375.57) and £302.26 (95% CI £187.19 to £417.32) for the standard-care group and intervention group, respectively. Background health-care costs, which include all health-care contacts not associated with an exacerbation and other prescribed medications, were £176.92 (95% CI £90.39 to £263.45) and £115.74 (95% CI £83.70 to £147.77) for the standard-care group and the intervention group, respectively.

In the base-case cost-effectiveness analysis, the expected cost and QALYs were slightly higher in the intervention group than in the standard-care group; however, these differences were very small (close to zero). When considering the uncertainty surrounding the expected differences, the probability of FeNO plus symptom-guided treatment offering a cost-effective approach compared with the standard symptom-guided treatment never rises higher than 48%, irrespective of the monetary value placed on a QALY.

Qualitative process evaluation

In the qualitative process evaluation, 15 trial staff and six families were interviewed. Interviews were audio-recorded and transcribed verbatim. A thematic approach was used to analyse the transcripts. Overall, experiences within both groups were positive. Key was that the RAACENO trial had a positive impact on staff–family relationships and communication around asthma management and treatment among children, and that the use of technology and individual data within clinical appointments was considered useful. Closer monitoring and the educational impacts were especially highlighted. We also ascertained that the intervention was broadly acceptable, with caveats around clinicians using the algorithm recommendation as a guide (rather than being dictated to by it) and wariness around extreme step ups/step downs in the light of contextual factors not taken into account by the algorithm.

Strengths and limitations

The RAACENO trial achieved the desired sample size, recruiting children with troublesome asthma as intended. The primary outcome was determined for 99% of participants. The computer-delivered treatment algorithm ensured that standardised care was recommended to all participants in all trial centres. There were clinically meaningful improvements in asthma control and quality of life in all participants.

A well-recognised cut-off point on a validated instrument was used to define uncontrolled asthma, but control is a continuum. The change in FeNO that triggered a change in treatment was based on the best evidence available, but this threshold might not have been correct. Children's adherence to IC medication may have been over reported. Treatment options in the two groups may not have been sufficiently different to create a difference in outcomes. Participants were predominantly under secondary care, where their management placed them at the lowest risk for future exacerbations, and the exacerbations that occurred may have been unavoidable. Treatment recommendations were not followed in approximately 25% of encounters.

Conclusions

The RAACENO trial findings do not support the routine use of FeNO measurements as part of childhood asthma management in a secondary care setting. The role of FeNO in managing childhood asthma in primary care remains to be formally evaluated. The potential for other objective markers to guide asthma management in children could be evaluated.

Trial registration

This trial was registered as ISRCTN67875351.

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