Temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations: FAST

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Scientific summary

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Scientific summary

Extracts of text throughout this Scientific summary have been published in Skeggs et al. [Skeggs A, McKeever T, Duley L, Mitchell E, Bradshaw L, Mortimer K, et al. Fourfold Asthma Study (FAST): a study protocol for a randomised controlled trial evaluating the clinical cost-effectiveness of temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations. Trials 2016;17:499. URL: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1608-6]. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

Background

Asthma is a chronic long-term condition estimated to affect 300 million people worldwide. Acute exacerbations of asthma are unpredictable, disruptive and frightening. The acute exacerbations cause considerable morbidity and account for a large proportion of the health service costs of asthma. The widespread use of an asthma self-management plan, designed to encourage disease monitoring and timely intervention, can reduce exacerbations and such plans are internationally recommended for all patients with asthma. Unfortunately, the majority of patients are not provided with a plan. There are a variety of reasons for this but uncertainty about what to include in the plan when asthma control is deteriorating but before the need for systemic corticosteroids is a contributing factor.

The aim of this trial was to determine whether or not an asthma self-management plan that included a temporary quadrupling of the dose of inhaled corticosteroid when asthma control started to deteriorate can reduce severe asthma exacerbations requiring systemic corticosteroids or an unscheduled health-care consultation for asthma compared with a standard self-management plan.

Objectives

Overall, the study assessed the comparative clinical effectiveness and cost-effectiveness of an asthma self-management plan that includes a temporary quadrupling of the dose of inhaled corticosteroid when asthma control starts to deteriorate at preventing an asthma exacerbation. Asthma exacerbation was defined as the need for systemic corticosteroids and/or an unscheduled health-care consultation for asthma.

The primary objective was to determine whether or not the proposed asthma self-management plan reduces asthma exacerbations.

The secondary objectives were to determine (1) whether or not the proposed asthma self-management plan reduces the deterioration in asthma control and (2) if the proposed asthma self-management plan is cost-effective to the NHS and society overall.

Methods

Study design

A multicentre, parallel-group, pragmatic randomised trial, with follow-up for 12 months. Adults were randomised (1 : 1) to follow either a usual-care self-management plan or a modified asthma self-management plan, which includes a temporary fourfold increase in inhaled corticosteroid when asthma control starts to deteriorate.
Recruitment
Participants were recruited from both primary and secondary care across England and Scotland, and through local advertising. Most participants (approximately 80%) were recruited within primary care.

Primary care recruitment was in general practices across England and Scotland in conjunction with Primary Care Research Networks [subsequently local Clinical Research Networks (CRNs)/Scottish CRNs], with practices acting either as Participant Identification Centres or as Research Initiative Sites (RISs). Participants were identified by database searches and invitation letters and by opportunistic recruitment via posters, social media and face-to-face discussions.

Secondary care recruitment was primarily from respiratory outpatient clinics and via specific research volunteer databases.

Eligibility

Inclusion criteria
Patients were considered eligible for entry into the trial if the following inclusion criteria were met:

- men or women aged ≥ 16 years
- clinician-diagnosed asthma treated with a licensed dose of inhaled corticosteroid [i.e. steps 2–4 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines]
- one or more asthma exacerbations in the last 12 months requiring treatment with systemic corticosteroids
- current smokers could be included provided that the recruiting centres had good evidence of underlying asthma (i.e. a life-long history of asthma, a > 12% forced expiratory volume in 1 second (FEV₁) reversibility, or sputum or blood eosinophilia).

Exclusion criteria

- A history more in keeping with smoking-related chronic obstructive pulmonary disease (i.e. smoked > 20 pack-years, without evidence of significant reversibility or blood eosinophilia).
- On maintenance systemic corticosteroids (i.e. step 5 of the BTS/SIGN guidelines).
- Using a combination inhaler for both maintenance and relief treatment.
- Experienced an exacerbation within 4 weeks of randomisation.
- Women who were pregnant, breastfeeding or who were planning to become pregnant.

Interventions
Participants were randomised equally (i.e. 1 : 1) to one of two asthma self-management plans (usual or modified) developed from the Asthma UK plan [Asthma UK. Asthma UK Asthma Action Plan. URL: www.asthma.org.uk/globalassets/health-advice/resources/adults/adult-asthma-action-plan.pdf (accessed 14 July 2017)] that was in use at the time of protocol development. In both the usual-care and modified plans, zones 1, 3 and 4 were identical and zone 2 included the current area of uncertainty and the research question under investigation.

At randomisation, participants were provided with asthma diary cards, which were to be completed for 14 days when their asthma deteriorated. On reaching zone 2 of the plan, the usual-care group were advised to increase their bronchodilator medication, as per current recommendations, for a maximum of 14 days, and the modified self-management group were advised to increase their bronchodilators and quadruple their inhaled corticosteroid dose.

Assessment of adherence to the two self-management plans included a review of the asthma diary card and questions about whether or not and how participants changed their inhaled corticosteroid treatment since activating zone 2 of their self-management plan (e.g. total number of puffs per inhaler, morning peak expiratory flow score, requirement for systemic corticosteroids).
Outcomes

The primary outcome of ‘time to first asthma exacerbation’ was defined as the need for systemic corticosteroids (for at least 3 consecutive days) and/or unscheduled health-care consultations for asthma (i.e. reaching zone 3 or 4 of the Asthma UK self-management plan).

Secondary outcomes included the use of systemic corticosteroids and unscheduled health-care consultations for an acute exacerbation of asthma (number of participants and total number of courses of systemic corticosteroids, unscheduled health-care consultations and exacerbations; time to participants requiring systemic corticosteroids and time to an unscheduled health-care consultation for an acute exacerbation of asthma), cumulative dose of inhaled and systemic corticosteroids used in the 12 months after randomisation, area under the morning peak flow curve over 2 weeks after activating zone 2 of the self-management plan and Juniper et al.’s (Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32–8) Asthma Quality of Life Questionnaire (Mini AQLQ). The cost and resource outcomes of both trial arms are reported as incremental cost per asthma exacerbation prevented and cost per quality-adjusted life-year (QALY) gained.

Sample size

With 2300 participants and using a log-rank test (at the two-sided 5% significance level), the study had at least 90% power to detect a difference of 30% (relative effect), assuming an exacerbation rate of 13% in the control group and allowing for loss to follow-up of around 15%. A 13% exacerbation rate requiring systemic corticosteroids, was the lowest level seen in the control group of previous studies of this type and so provided a conservative estimate.

Owing to the interim event rate for the primary outcome being higher than estimated, the power calculation was revised in March 2015. Assuming an exacerbation rate in the control group of 17%, 90% power and still estimating a one-third reduction in the modified self-management group, the sample size was revised to between 1750 and 1850 participants, allowing for loss to follow-up.

Randomisation and blinding

Randomisation was stratified by recruiting site (20 regional centres), smoking status (yes/no) and maintenance dose of inhaled corticosteroid dose (high/low).

This was an open-label clinical trial, so the participant and local study team were aware of the self-management plan allocation. Prior to database lock only the Data Monitoring Committee was able to review data according to treatment allocation, whereas the blinding allocation was preserved for the chief investigator, trial statisticians, the Nottingham Clinical Trials Unit trial management team and the Trial Steering Committee members.

Statistical methods

All analyses were based on the intention-to-treat principle, for example analysed as randomised regardless of adherence to a self-management plan. All participants were included in the analysis of the primary outcome apart from those with no further contact after randomisation, and for whom, therefore, information about oral corticosteroid use or unscheduled health-care consultations for asthma was unavailable. Cox proportional hazards regression model adjusting for randomisation stratification variables was used to analyse the primary outcome. Subgroup analyses, for smoking status at trial entry and high/low levels of inhaled corticosteroid use at trial entry, were also performed by including an interaction term in the Cox proportional hazards model.

Health economics

A cost-effectiveness analysis was undertaken to compare the modified self-management plan with the usual-care self-management plan. Following the National Institute for Health and Care Excellence’s guidelines, the analysis was conducted from the NHS and Personal Social Services perspectives, with costs expressed in Great British pounds for the financial year 2014–15. QALYs were estimated by calculating the area under the
curve, using utility scores measured by EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaires at baseline, and at the 6-month and 12-month follow-ups. As well as QALYs, the economic evaluation also determined cost-effectiveness results based on the total number of exacerbations per participant in the 12-month period.

The level of uncertainty associated with the decision over which option was most cost-effective was explored using the non-parametric bootstrapping method and presented using cost-effectiveness planes and cost-effectiveness acceptability curves.

**Results**

Recruitment to the study took place between 17 May 2013 and 29 January 2016. During this time, in excess of 20,695 patients were contacted and, subsequently, 4811 patients were assessed for eligibility. Of these 4811 patients, 1922 (40%) were randomised: 965 to usual self-management and 957 to the modified self-management.

Characteristics at baseline were well balanced between the two treatment groups.

The mean age of participants was 57 years [standard deviation (SD) 15 years] and 1305 (68%) were women. At trial entry, 1344 participants (70%) were using a combination inhaler and 1495 (78%) were classed as being on a low dose of steroids (i.e. ≤ 1000 mcg/day of beclometasone dipropionate).

**Primary outcome**

There were 938 (97%) participants in the usual-care group and 933 (97%) participants in the modified treatment group included in the analysis of the primary outcome. A total of 27 participants from the usual-care self-management group and 24 from the modified self-management group were excluded from the analysis because they withdrew consent on the day of randomisation or they experienced exacerbation on the day of randomisation or no further information was available following randomisation. The number of participants having an exacerbation of asthma in the year after randomisation was 484 (51.6%) in the usual-care group and 420 (45.0%) in the modified self-management group. The adjusted hazard ratio for the time to first asthma exacerbation in the modified self-management group compared with the usual-care group was 0.81 [95% confidence interval (CI) 0.71 to 0.92; \( p = 0.002 \)].

There was no evidence of a difference in the hazard ratio for time to asthma exacerbation in the modified self-management group compared with the usual-care group according to smoking status or dose of maintenance inhaled steroid dose at baseline.

**Secondary outcome**

The number of participants using systemic corticosteroids [adjusted risk difference (RD) −7.0%, 95% CI −11.3% to −2.7%], having an unscheduled health-care consultation (RD −6.8%, 95% CI −11.1% to −2.4%) and an exacerbation (systemic corticosteroids or an unscheduled health-care consultation, RD −6.7%, 95% CI −11.2% to −2.3%) was lower in the modified self-management group than in the usual-care group.

Similarly, the total number of courses of systemic corticosteroids [adjusted incidence rate ratio (IRR) 0.82, 95% CI 0.70 to 0.96], unscheduled health-care consultations [adjusted IRR 0.86, 95% CI 0.75 to 0.99] and exacerbations [adjusted IRR 0.88, 95% CI 0.77 to 1.01] per participant was lower in the modified self-management group than in the usual-care group.

**Safety outcome**

The usual-care group experienced a higher incidence of serious adverse events (SAEs) than the modified self-management group, with 22 participants (4%) in the usual-care group and 11 participants (2%) in the
modified self-management group who activated zone 2 or above experiencing at least one SAE. Eighteen of the 32 SAEs in the usual-care group were as a result of hospitalisations for asthma, compared with 3 of the 11 SAEs in the modified self-management group. Eight and six events of pneumonia, lower respiratory tract infections or influenza were reported as SAEs in the usual-care group and the modified self-management group, respectively.

More incidents of known side effects of inhaled corticosteroids were reported by the participants in the modified self-management group [collected as adverse events (AEs)]. Ten participants in the usual-care group (2%) and 41 participants in the modified self-management group (7%) who activated zone 2 or above had at least one known adverse effect of inhaled corticosteroids, such as oral candidiasis and dysphonia. Of the 56 non-serious AEs in the modified self-management group, 44 were classified as definitely or probably related to inhaled corticosteroids, compared with 6 of the 13 non-serious AEs in the usual-care group.

**Health economic outcome**

The modified self-management group had a lower total reported cost per participant than the usual-care group (£415 vs. £431, respectively); this was mostly driven by the difference in health-care resource use. This resulted in modified self-management being £24 (bootstrapped 95% CI =£122 to £71) less costly than usual care; however, this difference did not reach statistical significance (p = 0.681).

There was little difference between the QALY scores for the two groups at baseline, and both groups’ scores declined over the duration of the study period. The resulting difference in the QALY was 0.02 (bootstrapped 95% CI =0.005 to 0.04) greater for the modified self-management group after adjusting for baseline EQ-5D-3L scores; however, this difference was not statistically significant (p = 0.207).

The mean number of exacerbations was also lower in the modified self-management group [0.84 exacerbations, standard error (SE) = 0.04] than in the usual self-management group (0.95 exacerbations, SE = 0.04) with an adjusted difference of 0.10 (bootstrapped 0.95% CI =–0.22 to 0.01) exacerbations. As the modified treatment was both less costly and more effective for both health outcomes, the modified treatment was said to be ‘dominant’. This was supported by the uncertainty analysis showing a 94–95% probability of the modified treatment being cost-effective at the £20,000–30,000 threshold.

**Conclusions**

**Implications for health care**

The trial has demonstrated that a temporary quadruple increase in the dose of inhaled corticosteroid at the point when asthma control starts to deteriorate can prevent severe asthma exacerbations when compared with the usual-care self-management plan. A temporary quadrupling, rather than usual self-management, is also associated with fewer unscheduled health-care consultations, courses of prescribed systemic corticosteroids and reported asthma-related hospitalisations.

The economic analysis found that participants who received the modified treatment had, after adjusting for covariates, non-significantly lower total mean costs over the 12-month period. The evidence showed that quadrupling the inhaled corticosteroid dose at the point of asthma worsening did result in better clinical outcomes and was supported by the economic analysis.

**Recommendations for practice**

The trial has shown that the use of an asthma self-management plan that advises patients to quadruple their dose of inhaled corticosteroid at the point of asthma deterioration is effective in reducing exacerbations and should be considered by clinical commissioners as being embedded into routine general practice for asthma patients who exacerbated in the last year. It was calculated that 15 patients need to be taught to use such a plan to prevent one exacerbation or unscheduled health-care consultation.
Trial registration

This trial is registered as ISRCTN15441965.

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