Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial

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Summary

Background Treatment decisions in asthma are based on assessments of symptoms and simple measures of lung function, which do not relate closely to underlying eosinophilic airway inflammation. We aimed to assess whether a management strategy that minimises eosinophilic inflammation reduces asthma exacerbations compared with a standard management strategy.

Methods We recruited 74 patients with moderate to severe asthma from hospital clinics and randomly allocated them to management either by standard British Thoracic Society asthma guidelines (BTS management group) or by normalisation of the induced sputum eosinophil count and reduction of symptoms (sputum management group). We assessed patients nine times over 12 months. The results were used to manage those in the sputum management group, but were not disclosed in the BTS group. The primary outcomes were the number of severe exacerbations and control of eosinophilic inflammation, measured by induced sputum eosinophil count. Analyses were by intention to treat.

Findings The sputum eosinophil count was 63% (95% CI 24–100) lower over 12 months in the sputum management group than in the BTS management group (p=0.002). Patients in the sputum management group had significantly fewer exacerbations than patients in the BTS management group (35 vs 109; p=0.01) and significantly fewer patients were admitted to hospital with asthma (one vs six, p=0.047). The average daily dose of inhaled or oral corticosteroids did not differ between the two groups.

Interpretation A treatment strategy directed at normalisation of the induced sputum eosinophil count reduces asthma exacerbations and admissions without the need for additional anti-inflammatory treatment.

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Introduction

Asthma is characterised by variable airflow obstruction, airway hyper-responsiveness, and chronic airway inflammation, which is generally eosinophilic. It is a common disease that can cause much morbidity and mortality. Although bronchodilators and moderate doses of regular inhaled steroids provide good control for most individuals with asthma, some develop severe exacerbations that are difficult to prevent and can lead to time off work, admission to hospital, and life-threatening attacks. Management decisions in asthma have traditionally been based on assessment of symptoms, airway function, and use of rescue $\beta_2$ agonists. These features do not relate closely to the underlying eosinophilic airway inflammation and, consequently, clinicians cannot always predict the nature and extent of lower airway inflammation in patients with symptomatic asthma.

Eosinophils are thought to have an important pro-inflammatory role in the pathogenesis of asthma. Eosinophils and their mediators are consistently identified in asthmatic but not healthy lungs, and suppression of eosinophil infiltration in clinical disease by glucocorticoids is usually associated with an amelioration of symptoms and disordered airway function. Although use of antibodies to interleukin 5 do not lend support to a role for eosinophils in development of early or late responses to allergen challenge, eosinophils are probably associated with asthma exacerbations. Furthermore, sputum eosinophilia develops several weeks before the onset of an exacerbation. We therefore postulated that a management strategy that controls lower airway eosinophilic inflammation and symptoms would result in fewer exacerbations than would a traditional approach. Development of non-invasive techniques to assess airway inflammation has made it feasible to investigate such an approach to management of asthma.

Methods

Patients

We invited all patients aged 18–75 years who had a diagnosis of asthma and were thought to need continued hospital follow-up to participate. All patients were attending one of three specialist clinics at Glenfield Hospital, Leicester, UK, between March and October, 2000. We excluded patients if they were current smokers, had a smoking history of more than 15 pack years, or if they had clinically important comorbidity. We also excluded patients who were considered by their physician to comply poorly with treatment; had aggravating factors that were inadequately controlled, such as rhinitis or gastro-oesophageal reflux; or had had a severe exacerbation within 4 weeks of entry to the trial. Thus, we maximised the chance that current symptoms were due to asthma and that the patients were stable and would take treatment as instructed during the trial. Severe exacerbations were defined as a decrease in the morning peak expiratory flow to
more than 30% below the baseline value on 2 or more consecutive days, or deterioration in symptoms needing treatment with oral corticosteroids.11 All patients had symptoms consistent with a diagnosis of asthma and one or more of: a greater than 15% increase in forced expiratory volume (FEV₁) after 200 μg inhaled salbutamol; more than 20% variability in peak expiratory flow within a day, assessed twice daily baseline over 2 weeks; or a concentration of methacholine causing a 20% fall in FEV₁, (methacholine PC₂₀) of less than 8 g/L. The study was approved by the local research ethics committee and all patients gave written informed consent.

**Procedures**

After recruitment, we recorded baseline characteristics, and patients then underwent a 2 week run-in period during which they were maintained on their usual treatment. For baseline measurements, we used symptom scores, peak flow measurements, and use of rescue treatment during the final week of the run-in period. If during the run-in period they had nocturnal waking, daytime symptoms on 4 or more days, or a peak expiratory flow of less than 80% of that predicted on 2 or more consecutive days, then the patients had a further 2 week run-in period during which, to maximise their asthma control, they received 30 mg oral prednisolone a day in addition to their usual treatment. In these patients, the second week of this run-in period was then used as baseline. At the end of the run-in period, we randomly allocated patients to either management by a modified version of the British Thoracic Society guidelines (BTS management group) or management with reference to the induced sputum eosinophil count (sputum management group). Randomisation was done by an independent individual (CEB) with the method of minimisation,12 and was stratified by the number of rescue courses of oral corticosteroids used in the previous 12 months, the baseline induced sputum eosinophil count, and the baseline methacholine PC₂₀.

Patients were followed up for 12 months after randomisation, with one visit a month for the first 4 months and one visit every 2 months thereafter. Decisions about asthma control were made per protocol by investigators who were unaware of the patients’ randomisation status (SM, BH), and management decisions were made by an independent physician who was unaware of the sputum eosinophil count in the BTS management group (RHG) and of the clinical control in the sputum management group (IDP). Neither the patients nor their physicians were aware of their management groups and neither had any knowledge of treatment protocols. All patients underwent identical investigations and were contacted 3–5 days after the clinical visits with treatment instructions. Patients and their physicians were encouraged to treat asthma exacerbations in the standard way as per the British Thoracic Society asthma guidelines and patients were issued with individualised self-management plans.1 At the end of the study, patients were asked to record which group they were in, and their treatment outcomes were compared with baseline—using the same criteria as in the BTS management group. Management decisions were made by an independent individual (IDP) who was unaware of the clinical characteristics of the patient, and who recorded separate treatment plans to be followed depending on whether the patient’s asthma was controlled well or poorly. When the patient could not produce sputum, we used the exhaled concentration of nitric oxide as a surrogate marker of eosinophilic airway inflammation.13 Treatment was targeted to achieve an exhaled nitric oxide (NO) concentration of less than 8 parts per billion. We assigned treatments as anti-inflammatory or bronchodilator on the basis of known pharmacological effects and evidence of the effects of treatment on eosinophilic airway inflammation.15–17 The panel shows the hierarchy of anti-inflammatory and bronchodilator treatment used in the sputum management group.

At entry we did allergen skin prick tests and recorded details of smoking status, current treatment, duration of asthma, courses of rescue corticosteroids, and admissions in the previous year from patients’ histories corroborated by clinical records. Patients attended at the same time of day on each occasion, 4–6 h and 24 h after the last doses of short-acting and long-acting β₂ agonists, respectively. At every visit we assessed patients by measurement of exhaled concentrations of NO, spirometry before and after 200 μg inhaled salbutamol, the asthma quality-of-life questionnaire,8 visual analogue scale symptom scores, and sputum induction for differential cell count. The order and timing of investigations was standardised. We assessed methacholine PC₂₀, instead of bronchodilator reversibility at the baseline, 6 month, and 12 month visits unless patients were seen within 2 weeks of a severe exacerbation or the FEV₁ was 1 L or less.

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1. BTS guidelines modified in the following way: as required by clinical records. Patients attended at the same time of day on each occasion, 4–6 h and 24 h after the last doses of short-acting and long-acting β₂ agonists, respectively. At every visit we assessed patients by measurement of exhaled concentrations of NO, spirometry before and after 200 μg inhaled salbutamol, the asthma quality-of-life questionnaire,8 visual analogue scale symptom scores, and sputum induction for differential cell count. The order and timing of investigations was standardised. We assessed methacholine PC₂₀, instead of bronchodilator reversibility at the baseline, 6 month, and 12 month visits unless patients were seen within 2 weeks of a severe exacerbation or the FEV₁ was 1 L or less.

**ARTICLES**

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Treatment hierarchy for sputum management group

**Anti-inflammatory treatment**

1. Low-dose inhaled steroid: 100–200 μg beclometasone or equivalent, twice a day
2. Moderate-dose inhaled steroid: 200–400 μg beclometasone or equivalent, twice a day
3. High-dose inhaled steroid: 400–800 μg beclometasone or equivalent, twice a day
4. Higher-dose inhaled steroid: 1600 μg beclometasone or equivalent, twice a day
5. Higher-dose inhaled steroid: 1600 μg beclometasone or equivalent, twice a day, plus leukotriene antagonist
6. Higher-dose inhaled steroid: 1600 μg beclometasone or equivalent, twice a day, plus 30 mg oral prednisolone for 2 weeks
7. Higher-dose inhaled steroid: 1600 μg beclometasone or equivalent, twice a day, plus oral 30 mg prednisolone for 2 weeks followed by maintenance oral prednisolone titrated to sputum eosinophil count

**Bronchodilator treatment**

1. Long-acting β₂ agonist
2. Long-acting β₂ agonist plus theophylline
3. Long-acting β₂ agonist plus theophylline and nebulised bronchodilator

*Patients with sputum eosinophils of 3–10% start with treatment 1 or 2; with sputum eosinophils 10–30% start with treatment 3 or 4; and with sputum eosinophils >30% start with treatment 5 or 6.

We did allergen skin prick tests to *Dermatophagoides pteronyssinus*, cat fur, grass pollen, and *Aspergillus fumigatus* solutions with normal saline and histamine controls (Alk-Abelló, Berkshire, UK). End-exphaled NO was measured with a chemiluminescence analyser (Logan Research, Rochester, UK) with patients exhaling at a flow rate of 250 mL/s from total lung capacity over 30–40 s. NO was sampled from a sidearm attached to the mouthpiece and the mean NO value was taken from the point corresponding to the plateau of the end-exphaled carbon dioxide reading. Methacholine challenge testing was done with the tidal breathing method with doubling concentrations of methacholine (0·03–16·00 g/L) nebulised via a Wright nebuliser (Fisons Pharmaceuticals, Loughborough, UK). We recorded symptoms on 100 mm visual analogue scales (from 0–300 mm) was the sum of the visual analogue score (from 0–300 mm) for breathlessness, wheeze, and cough. The total score was from no symptom (0 mm) to the worst ever symptom (100 mm). A skilled observer (DP) who was unaware of the clinical characteristics of the patients did the cell counts within 4 days of the clinic visits. Patients completed daily diary cards throughout the study, and recorded daytime and night-time symptoms, twice a day before bronchodilator peak expiratory flow, drug use including rescue β₂ agonist and oral prednisolone, days off work, and emergency care visits. Peak expiratory flow was recorded as the best of three successive readings using a Mini-Wright peak-flow meter (Clement Clarke International Ltd, Harlow, UK). Symptom scores ranged from 0 to 3 (for daytime symptoms: 0=none, 1=occasional symptoms, 2=severe symptoms most of the day, 3=asthma very bad, unable to do usual activities at all; for night-time symptoms 0=none, 1=awoke once due to asthma, 2=awoke 2–3 times due to asthma, 3=awoke most of the night due to asthma). In both groups we assessed compliance with clinical impression, and tablet counting, prescription checking, weighing of inhalers, and monitoring of serum prednisolone or theophylline concentrations where there was any doubt.

Statistical analysis

A power calculation, based on our own observations of the frequency of exacerbations in a similar group of patients with asthma attending our clinics (mean exacerbations 3·2 [SD 2·1] per patient per year), showed that we needed 30 patients in each group to show a 50% reduction in severe exacerbations (α=0.05, β=0.2). The primary outcomes were the number of severe asthma exacerbations and control of eosinophilic airway inflammation measured by the induced sputum eosinophil count. Secondary outcomes were exhaled NO concentrations, symptom scores, total asthma quality-of-life scores, peak flow amplitude as a proportion of the mean, FEV₁, change from baseline of methacholine PC₂₀, drug use, and admissions for asthma. If patients withdrew because of poor asthma control, we analysed their data by intention to treat and extrapolated it for the 12-month follow-up period; we included data from patients who withdrew for other reasons until the time of withdrawal. We compared differences in severe asthma exacerbations with the Mann-Whitney *U* test and the daily doses of inhaled and oral corticosteroids by an independent *t* test. Additional treatments were not used by all patients, but when they were used, the dose was constant. Therefore, we compared proportions of patients receiving each type of additional treatment, the proportion having one or more exacerbations, and the proportion having an admission due to asthma with the χ² test. We used the independent *t* test to compare change from baseline in methacholine PC₂₀ and the area under the curve between groups for all other variables over the 12 months. Post-hoc analyses of the between-group differences in the change from baseline in inhaled and oral corticosteroid doses in non-eosinophilic and eosinophilic subgroups was also done by an independent *t* test. Doses of inhaled corticosteroid have been expressed as beclometasone dose equivalents (with fluticasone considered to be twice as potent and budesonide equipotent). The overall cost of each management strategy was calculated with our estimates of the cost of sputum induction and processing (US$24 per sample), the 2001 Unit Costs of Health and Social Care,21 the Department of Health 2001 reference costs,22 and the British National Formulary (September, 2001). We calculated the total costs for patients by the sum of the costs of hospital out-patient appointments, primary care visits, admissions, and drug use over the 12 months, with the addition of the costs of sputum induction and processing for patients in the sputum management group only. We then compared mean costs with an independent *t* test.23 p values of less than 0.05 were judged significant. All data were analysed with SPSS for Windows (version 10.0).

**Role of the funding source**

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

**Results**

We recruited 82 patients, of whom 74 were allocated to a management group; eight patients withdrew during the run-in period and a further six patients withdrew during follow-up, leaving 34 patients in each group who completed the study (figure 1). No patient withdrew because of poor asthma control. The two treatment groups were matched at baseline for demographic and clinical features and similar numbers of patients in each group received an oral corticosteroid trial (table).

Sputum induction was successful in 552 of 632 attempts (87%). Assessed over the 12 months as the area under the...
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Significantly fewer patients in the sputum management group were admitted because of exacerbations of asthma (one vs six; \(p=0.047\)).

Visual analogue symptom scores, total asthma quality of life scores, peak expiratory flow amplitude as a proportion of mean, FEV\(_1\) after bronchodilator use, and use of rescue \(\beta_2\)-agonists did not differ between the two groups (figure 4). Significantly fewer patients in the sputum management group than in the BTS management group received nebulised bronchodilators (four vs 11; \(p=0.043\)). The same number of patients in both groups were given long-acting \(\beta_2\)-agonists (12 vs 12; \(p=1.0\)), leukotriene antagonists (13 vs 15; \(p=0.63\)), and theophylline (12 vs 12; \(p=1.0\)). The mean dose of inhaled corticosteroids or oral prednisolone did not differ between groups (inhaled corticosteroids, 1660 g (SE 215) vs 1705 g (189) per patient per day, \(p=0.88\); prednisolone, 2.6 mg (0.6) vs 3.0 mg (0.8) per patient per day, \(p=0.69\)).

13 patients in the sputum management group and 11 in the BTS management group had a geometric mean sputum eosinophil count across the 12 months that was within the normal range (<1.9%). In subgroup analysis of these patients with non-eosinophilic inflammation, management by sputum guidelines resulted in a 961 g per patient per day reduction in the inhaled corticosteroid dose at the end of the study compared with baseline, whereas in the BTS management group, inhaled corticosteroids were increased by 464 g per patient per day (mean difference 1425 g [95% CI 529–2329] per patient per day; \(p=0.001\)). The number of exacerbations and the change in PC\(_{20}\) did not differ between these subgroups (\(p=0.47\) and \(p=0.20\), respectively).

When asked to document which randomisation group they thought they had been assigned to, 54% of patients recorded “don’t know”, 28% of patients selected the correct group, and 18% were incorrect. The proportion of responses was similar between the two groups.

The estimated yearly mean cost per patient was US$3082 (SE 259) for the BTS management group and $2768 (188) for the sputum management group (\(p=0.30\)).

**Discussion**

Severe exacerbations of asthma needing courses of oral corticosteroids or admission are the most serious manifestation of this disease. They lead to asthma deaths, patient morbidity, and a high cost to the health service in...
terms of doctor consultations, drug use, and hospital beds. Our results show that a strategy directed at maintenance of a normal airway eosinophilic count caused a large reduction in the number of severe exacerbations in a group of patients with moderate to severe asthma attending our outpatient clinic compared with traditional management based on the BTS guidelines. We believe such an effect has implications for management of asthma in that it strongly supports the view that airway inflammation should be monitored regularly for optimum treatment of this group of patients.

Our results also lend support to a central role for eosinophils in the pathogenesis of asthma. The idea that eosinophils are important proinflammatory cells in asthma has not been supported by results of a study in which human monoclonal antibodies to interleukin 5 reduced sputum eosinophilia after allergen challenge, but had no effect on the early or late fall in FEV1 or on airway responsiveness. In addition, airway eosinophilia can be dissociated from airway responsiveness and variable airflow obstruction in asthma. Airway hyper-responsiveness is more closely associated with mast-cell infiltration of the airway smooth muscle than with presence of eosinophils, basement membrane thickening, and activated TH2 cells in the airway submucosa. However, the pathophysiology of severe asthma exacerbations is complex and includes mucosal oedema, mucous hypersecretion, and decrease of the lumen of the bronchi by impaction with cellular debris as well as smooth muscle contraction. Our results lend support to a crucial role for eosinophils in this process by showing that a reduction in eosinophils after use of glucocorticoids prevented exacerbations. Although such an association is not proof of cause and the effect could be mediated through another corticosteroid-sensitive mechanism, our findings suggest that eosinophilic airway inflammation is a more valid surrogate marker of exacerbation frequency than are the other outcome measures assessed in this study. A key question is whether antibodies to interleukin 5, which has a more specific effect on eosinophilic inflammation, is able to reduce the number of severe exacerbations.

Eosinophilic airway inflammation and airway responsiveness tended to increase in the traditional management group and post bronchodilator FEV1 measurements after bronchodilator use declined in both groups, presumably reflecting regression towards the mean and the effects of the oral corticosteroid trial during the run-in period on early measurements. This effect was not seen with symptoms, use of β2 agonists, and variability in peak flow. Moreover, the improvement in eosinophilic airway inflammation and exacerbation frequency in the sputum management group was not associated with improvements in these traditional markers of asthma control. These observations lend further support to the idea that the mechanisms causing exacerbations and eosinophilic airway inflammation can be dissociated from those that underlie symptoms and variable airflow obstruction. That higher doses of inhaled steroids are more effective in controlling exacerbations but less effective at controlling symptoms and peak flow variability compared with addition of long-acting β2 agonists is consistent with this view. This apparent dissociation between control of inflammation, exacerbations, and symptoms or variable airflow obstruction has important implications for management of asthma, suggesting, for example, that a traditional approach in which a new treatment is discontinued if the patient’s symptoms and peak expiratory flow do not improve needs to be reconsidered.

Our definition of an exacerbation was based on the definition of severe exacerbations used in the FACET study. We noted more exacerbations in our study than did the investigators of the FACET study, probably because our patients had more severe disease and because we did not exclude patients who had frequent exacerbations. The increased frequency of exacerbations could also have been due to misclassification of periods of poor asthma control. Reidel and colleagues have suggested that periods of poor asthma control can be distinguished from exacerbations because they are associated with increased symptoms, increased variability in peak expiratory flow, and increased response to β2 agonists. We doubt that the improved outcome seen in the sputum management group resulted from reductions in periods of poor asthma control rather than exacerbations since control of symptoms and variability in peak expiratory flow did not differ between the two groups.

That control of eosinophilic airway inflammation and exacerbations was greater in the sputum management group than in the BTS management group without any increase in overall treatment could have been because treatment was reduced more quickly in this group. However, in an exploratory post-hoc analysis, several patients had a sputum eosinophil count that was mostly within the normal range throughout the study. In these patients, the dose of corticosteroids was greatly reduced in the sputum management group without evidence of deterioration in control. By contrast, in patients with eosinophilic inflammation, the doses of inhaled and oral corticosteroids were increased in both treatment groups, although the doses were probably increased before exacerbations started in the sputum management group and in response to exacerbations in the BTS management group. Thus, monitoring of airway inflammation allowed treatment to be targeted and used more efficiently. We have previously identified a group of patients without a sputum eosinophilia but with symptomatic asthma and have associated the absence of sputum eosinophils with a poor response to short-term treatment with inhaled corticosteroids. Our results provide some support for the presence of an asthma phenotype that is non-eosinophilic and resistant to corticosteroids, and provide new evidence that it is stable in the long term.

The sputum management protocol resulted in improved airway responsiveness at 6 months and 12 months. Results of the AMPUL study showed that an asthma management strategy targeted to improve airway responsiveness results in reduced asthma exacerbations when compared with traditional management. The improved outcome seen in this study could have been due to improvement in eosinophilic airway inflammation since the active management group received significantly higher doses of inhaled corticosteroids and had improved bronchoscopic measures of airway inflammation at the end of the study compared with those in the control management group. However, we cannot exclude the possibility that a treatment strategy that targets both airway responsiveness and eosinophilic inflammation could achieve even better results.

Our study had several limitations. First, we could not do this study in a true double-blind fashion. However, management decisions were made strictly in accordance with the protocol and without knowledge of the sputum eosinophil count in the BTS management group or of clinical control in the sputum management group. Furthermore, courses of rescue corticosteroids (accounting for two-thirds of asthma exacerbations) were almost always started by the patients or their physicians who were unaware of the randomisation status, so bias from non-blinding probably did not have an important effect on our results. Second, the protocol for the sputum management group...
could have been biased to achieve more rapid control of airway inflammation, thus accounting for the improved outcomes in this group. However, the differences in exacerbation frequency did not lessen with time. Nevertheless, less obvious differences in exacerbation frequency might have been seen if the study had been longer. Third, our criteria for assessment of clinical control were arbitrary, as in previous studies, and although equivalent and effective symptom control was achieved, we cannot exclude the possibility that tighter control would have reduced the difference seen in the frequency of exacerbations. Finally, we restricted our study to patients attending a specialist hospital clinic who were thought to be compliant—a high proportion of whom had refractory asthma. These patients were especially likely to benefit from the sputum management strategy since there is evidence of a heterogeneous lower airway inflammatory response.33,31 In addition, severe eosinophilic airway inflammation has been associated with reduced perception of bronchoconstriction in similar populations.32 Thus, although our management strategy is feasible, cost effective, and efficacious in secondary care, we would be cautious in extrapolation of our findings to patients with milder disease managed in primary care. We would also have reservations about the feasibility of inducing sputum in a primary care setting, although exhaled NO would be more suitable and further studies are needed to prospectively assess use of this procedure in management of asthma.

Contributors
R Green assisted with the protocol development, undertook study protocol development and recruitment, and did the analysis, and prepared the report. C Brightling designed the protocol and obtained funding for the study, did the randomisation and revised the report. S McKenna and B Hargadon assisted with the protocol development, and revised the report. D Parker analysed the induced sputum and reviewed the report. P Bradding and A Wardlaw obtained funding for the study, assisted with study protocol development and study recruitment, and revised the report. Ian Pavord designed and obtained funding for the study, and supervised clinical and laboratory assessments, study analysis, and preparation of the report.

Conflict of interest statement
None declared.

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