Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids

R H Green, C E Brightling, G Woltmann, D Parker, A J Wardlaw, I D Pavord

BACKGROUND: The debate as to whether asthma is a single or heterogeneous disease remains unresolved although pathological studies, mostly using fibreoptic bronchoscopy on small numbers of subjects, have emphasised the similarities between different clinical phenotypes.

METHODS: Lower airway inflammation was assessed non-invasively using induced sputum in 34 normal controls and 259 adults with symptomatic asthma receiving treatment at steps 1–3 of the British Thoracic Society (BTS) guidelines. A subgroup of 49 patients treated with as required β2 agonists only who met BTS criteria for a step up in treatment were studied before and 2 months after treatment with inhaled budesonide 400 µg twice daily.

RESULTS: There was considerable heterogeneity in induced sputum cell counts, particularly in non-atopic patients. A subgroup of 60 patients had a distinctive sputum cell profile with a neutrophil count higher than our normal range (>65.3%) and a normal sputum eosinophil count (<1.9%). These patients were older, predominantly female, and were more likely to be non-atopic but otherwise had similar clinical and physiological features to the group as a whole. Among the 49 subjects studied before and after inhaled budesonide, 11 patients had an isolated sputum neutrophilia. Following treatment, these patients showed significantly less improvement in visual analogue symptom scores (–5.5 v –19.4 mm; mean difference 13.9; 95% CI 0.7 to 27.0), forced expiratory volume in 1 second (FEV1) (–0.08 ± 0.13 l; mean difference 0.21; 95% CI 0.03 to 0.39), and concentration of methacholine provoking a fall in FEV1 of 20% or more (PC20) (0.15 v 1.29 doubling doses; mean difference 1.11; 95% CI 0.13 to 2.15) than the remaining 38 patients.

CONCLUSIONS: These results suggest the presence of a distinct subgroup of patients with mild to moderate asthma who have predominantly neutrophilic airway inflammation and who respond less well to treatment with inhaled corticosteroids.

ORIGINAL ARTICLE

Clinicians have long regarded asthma as a heterogeneous disease, although detailed clinicopathological studies have tended to emphasise the similarities in the underlying airway pathology and disordered function between patients. Airway inflammation in asthma has usually been assessed invasively using bronchoscopic techniques, so studies are largely confined to young adults with mild atopic asthma. Whether the findings can be generalised to a wider more heterogeneous population analogous to that seen in clinical practice is unclear.

More recent studies where airway inflammation has been measured non-invasively using induced sputum in a more diverse range of patients have shown predominant neutrophilic airway inflammation in some patients with severe asthma and in others studied during acute exacerbations. Whether these changes reflect the severity of the disease or the effect of treatment is unclear. We have measured airway inflammation in 34 normal and 259 subjects with symptomatic asthma receiving treatment at British Thoracic Society (BTS) steps 1–3 and have related sputum cell counts to the response to inhaled corticosteroids in 49 subjects. We have used these data to test the hypothesis that a predominant neutrophilic airway inflammation is present in a subset of patients with milder asthma and that this phenotype is associated with a poor response to inhaled corticosteroids.

METHODS

Subjects

Patients and controls were recruited from patients, staff, and volunteers attending the Department of Respiratory Medicine at the Glenfield Hospital. Normal controls had no symptoms suggestive of asthma, were non-smokers or ex-smokers who had not smoked within 12 months of study entry and had a past history of less than 10 pack years, had normal spirometric values (forced expiratory volume in 1 second (FEV1) >80% predicted and ratio of FEV1 to forced vital capacity (FVC) >80%), and normal methacholine airway responsiveness (PC20 >16 mg/ml). Subjects with asthma had consistent symptoms and one or more of the following: a methacholine PC20 of <8 mg/ml; a >15% increase in FEV1 10 minutes after 200 µg salbutamol or a >20% maximum within day variability in peak expiratory flow (PEF) measured twice daily over 14 days. Patients had no clinical or radiological evidence of bronchiectasis and no symptoms suggesting acute lower respiratory tract infection within a month of entering the study. All patients had an FEV1 % predicted of >65% and a smoking history of less than 10 pack years. Clinical records were used to corroborate patients’ smoking histories and exhaled carbon monoxide was measured where there was any doubt.

All patients with asthma treated at BTS steps 1–3 attending our respiratory outpatient clinic who fulfilled the entry criteria and who agreed to participate were included. Assessments were carried out following informed consent as part of a project examining the validity, repeatability, and responsiveness of induced sputum differential inflammatory cell counts which was approved by the Leicestershire Hospitals research ethics committee.
Study design and protocol

Patients and controls attended on two occasions. On the first occasion allergen sensitivity was measured by radioallergosorbent tests for specific IgE or skin prick testing to *Dermatophagoides pteronyssinus*, cat fur, grass pollen, and *Aspergillus fumigatus* and atopy was defined as one or more positive skin tests (weal >2 mm larger than negative control) or raised specific IgE (>0.34 kU/l) to one or more antigen. Spirometric tests before and after inhaled salbutamol and chest radiography were performed. Subjects recorded PEF twice daily as the best of three blows over a 14 day period.

On the second visit methacholine airway responsiveness was measured using the tidal breathing method followed, after recovery, by sputum induction and processing as previously described. The duration of inhalation of hypertonic saline was standard. A subgroup of patients taking as required β₂ agonists only who met the BTS criteria for a step up in treatment (using rescue β₂ agonists more than once per day, having nocturnal waking or limitations in activities, peak flow variability ≥20%, or PEF <80% of predicted or best) were given inhaled budesonide 400 µg twice daily for 2 months. These patients identified their predominant symptom (breathlessness, wheeze, or cough) and the severity of this was assessed using a 100 mm visual analogue scale (VAS) from (breathlessness, wheeze, or cough) and the severity of this was assessed using a 100 mm visual analogue scale (VAS) from (Dermatophagoides pteronyssinus) and atopy was defined as one or more positive skin tests (weal >2 mm larger than negative control) or raised specific IgE (>0.34 kU/l) to one or more antigen. Spirometric tests before and after inhaled salbutamol and chest radiography were performed. Subjects recorded PEF twice daily as the best of three blows over a 14 day period.

The patients then attended for a third visit when the spirometric tests, methacholine inhalation test, and VAS symptom scores were repeated 12 hours after the last dose of treatment. Data from some of these patients have been presented previously.

### Analysis of data

Normal ranges were derived from the eosinophil and neutrophil counts of the control subjects as the mean + 2SD and the mean + 1.75SD using one tailed and two tailed tests, respectively. One tailed tests were used for eosinophil counts since there is no lower reference limit. Spirometric values, induced sputum macrophage, neutrophil, lymphocyte and epithelial differential cell counts and maximum PEF amplitude % mean were described as mean (SE) values. Methacholine PC₂₀ results were log normally distributed and were log transformed and described as geometric mean (log SE) values. Sputum eosinophil counts were expressed as median and interquartile range (IQR). Differences between groups were analysed for normally distributed variables using the independent *t* test and for variables not observing a normal distribution using the Mann-Whitney *U* test. The correlation between sputum eosinophils and methacholine PC₂₀, PEF amplitude % mean (A%M), and FEV₁ were assessed using the Spearman rank test. Differences in methacholine PC₂₀ were expressed as doubling doses.

### RESULTS

#### All subjects

Normal ranges derived from normal subjects were <65.3% for sputum neutrophil counts and <1.9% for sputum eosinophil counts. 143 patients had intermittent asthma treated with required β₂ agonists only (step 1 of the BTS guidelines); 116 had more persistent symptoms requiring regular inhalated corticosteroids (steps 2 and 3) (table 1). Twenty patients (11% of the study population there was no correlation between the sputum eosinophil count and the methacholine PC₂₀, PEF amplitude % mean (A%M), and FEV₁ were assessed using the Spearman rank test. Differences in methacholine PC₂₀ were expressed as doubling doses. The χ² test was used to compare the percentage of patients using inhaled steroids and the percentage of atopic patients between groups.

#### Table 1 Patient details and sputum cell counts in normal controls, atopic and non-atopic subjects

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Atopic</th>
<th>Non-atopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>114</td>
<td>61</td>
<td>145</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63.8**</td>
<td>62.3**</td>
<td>34.0</td>
</tr>
<tr>
<td>Age</td>
<td>39 (21)**</td>
<td>40 (21)**</td>
<td>38 (38)**</td>
</tr>
<tr>
<td>Age at onset</td>
<td>16 (31)**</td>
<td>27 (38)**</td>
<td>11 (19)**</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>86.5 (1.4)</td>
<td>91.6 (1.6)</td>
<td>80.7 (2.4)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>73.8 (1.7)</td>
<td>73.1 (1.0)</td>
<td>73.0 (0.1)</td>
</tr>
<tr>
<td>Methacholine PC₂₀ (mg/ml)†</td>
<td>&gt;16</td>
<td>0.68 (0.07)**</td>
<td>0.89 (0.11)*</td>
</tr>
<tr>
<td>PEF amplitude % mean</td>
<td>26.0 (2.0)</td>
<td>22.2 (2.1)</td>
<td>30.1 (4.0)</td>
</tr>
<tr>
<td>Biologic eosinophils (%)</td>
<td>4.6 (0.4)</td>
<td>4.1 (0.4)</td>
<td>5.1 (0.8)</td>
</tr>
<tr>
<td>Sputum TCC (x 10⁵/ml)</td>
<td>2.8 (0.5)</td>
<td>2.3 (0.3)</td>
<td>2.3 (0.4)</td>
</tr>
<tr>
<td>Squamous cells (%)</td>
<td>4.4 (15.3)</td>
<td>3.8 (14.8)</td>
<td>4.7 (15.8)</td>
</tr>
<tr>
<td>Viability (%)</td>
<td>61.7 (2.0)</td>
<td>63.5 (2.7)</td>
<td>59.6 (3.3)</td>
</tr>
<tr>
<td>Eosinophils (%)†</td>
<td>3.0 (3.3)</td>
<td>45.0 (2.5)**</td>
<td>44.2 (3.1)**</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>61.0 (3.0)</td>
<td>43.5 (2.4)**</td>
<td>42.4 (3.0)**</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>1.4 (0.4)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>Epithelial cells (%)</td>
<td>3.8 (0.9)</td>
<td>3.2 (0.5)</td>
<td>3.2 (0.8)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Value</th>
<th>Mean (SE)</th>
<th>Geometric mean (log SE)</th>
<th>Median (IQR)</th>
</tr>
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<tbody>
<tr>
<td>FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; PC₂₀=concentration of methacholine provoking a fall in FEV₁ of 20% or more; TCC=total cell count. Values are mean (SE) except for †geometric mean (log SE) and ‡median (IQR).</td>
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<tr>
<td>Age 34 (16) 39 (21)** 40 (21)** 38 (38)** 53 (18)** 54 (25)** 50 (21)**</td>
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<td>Number 34 114 61 53 145 82 63</td>
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</tr>
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Notes: *p<0.05 atopic vs non-atopic subjects; **p<0.01 atopic vs non-atopic subjects.
Patients treated with as required β₂ agonists alone. A subgroup with isolated neutrophilic inflammation had an impaired response to inhaled corticosteroids. Furthermore, a subgroup of steroid naïve subjects with this isolated neutrophilic inflammation had an impaired response to treatment with inhaled corticosteroids.

Previous studies have noted sputum evidence of isolated neutrophilic airway inflammation in some patients with severe asthma and in a minority of adults studied during asthma exacerbations. Gibson et al used induced sputum to assess 56 patients with persistent asthma taking high doses of inhaled corticosteroids and found that 59% of patients had suppressed sputum eosinophil counts but evidence of neutrophilic inflammation. Wenzel et al used bronchoscopic techniques to characterise the underlying airway immunopathology of a group of patients with severe refractory asthma who had severely impaired lung function and were treated with high dose inhaled steroids and oral prednisolone and have suggested the presence of a subgroup who have a predominant neutrophilic airway inflammation, absence of eosinophils, and normal basement membrane thickness. It is not clear whether the findings are peculiar to severe asthma or reflect the effects of treatment with high doses of corticosteroids. Our results provide support for the presence of such a distinct asthma phenotype and, for the first time, show that it is a relatively common finding in patients with milder asthma and, in some subjects at least, that it is not an artefact due to corticosteroid treatment. The incidence of neutrophilic airway inflammation was higher in the population studied by Gibson et al and in the patients with severe asthma studied by Wenzel et al, and it remains possible that this phenotype is particularly associated with more severe disease. We have further extended these earlier findings by showing a significantly impaired response to inhaled corticosteroids in a subgroup of 60 patients, including 35 who were steroid naïve, had a distinctive sputum cell profile with a sputum neutrophil count outside the normal range and a normal sputum eosinophil count. Five of these were current smokers and 20 were ex-smokers. These patients were older, tended to develop asthma later, and were more likely to be female and non-atopic than the group as a whole. Clinical and physiological features were otherwise similar (table 2).

Patients studied before and after treatment with inhaled corticosteroids

Ninety two of the patients treated with as required β₂ agonists only met the BTS criteria for a step up in treatment. Forty nine such patients were randomly selected and agreed to attend again 2 months after treatment with inhaled budesonide 400 µg twice daily. Of these subjects, 11 were included in the subgroup described above, having an isolated sputum neutrophilia with a normal sputum eosinophil count (table 3). Compared with the other 38 patients studied before and after treatment, these subjects had significantly less improvement in VAS scores (−5.5 vs −19.4 mm; mean difference 13.9; 95% CI 0.7 to 27.0; p=0.04), FEV₁ (−0.08 vs 0.13 l; mean difference 0.21; 95% CI 0.03 to 0.39; p=0.026), and PC₂₀ (0.15 vs 1.29 doubling doses; mean difference 1.11; 95% CI 0.13 to 2.15; p=0.029; fig 1).

DISCUSSION

We have analysed the extent and nature of airway inflammation in induced sputum in normal controls and in a large population of well characterised patients with asthma. Our estimates of normal ranges, although derived from small numbers, are very similar to findings in larger populations. In the adults with asthma receiving treatment at BTS stages 1–3 and with relatively normal spirometric parameters, we found considerable heterogeneity in induced sputum inflammatory cell counts. Importantly, a number of predominantly female, non-atopic patients with adult onset asthma had a distinctive sputum inflammatory cell profile consisting of sputum neutrophilia and a normal sputum eosinophil count. We have also noted considerable heterogeneity in induced sputum eosinophil counts, even among those patients treated with as required β₂ agonists alone. A subgroup of 145 non-atopic patients demonstrated a weakly positive correlation between these two measurements (r=0.22, p<0.05).

Subgroup with isolated neutrophilic inflammation

There was considerable heterogeneity in induced sputum eosinophil and neutrophil cell counts, even among those patients treated with as required β₂ agonists alone. A subgroup of 145 non-atopic patients demonstrated a weakly positive correlation between these two measurements (r=0.22, p<0.05).
the subjects with an isolated neutrophilia. 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with inhaled corticosteroids and other treatments are also 
required to assess the efficacy of these interventions fully. Our 
findings raise the possibility of a distinct phenotype of 
asthma, with active neutrophilic and suppressed eosinophilic 
airway inflammation, across the range of severity of asthma 
that differs in response to treatment and could have important 
implications for our understanding and treatment of the dis-
case.

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LE3 9PQ, UK
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