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AUDIT UPDATE

Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry

Joan Sweeney,1 Chris E Brightling,2 Andrew Menzies-Gow,3 Robert Niven,4 Chris C Patterson,5 Liam G Heaney,1 on behalf of the British Thoracic Society Difficult Asthma Network

ABSTRACT

Refractory asthma represents a significant unmet clinical need. Data from a national online registry audited clinical outcome in 349 adults with refractory asthma from four UK specialist centres in the British Thoracic Society Difficult Asthma Network. At follow-up, lung function improved, with a reduction in important healthcare outcomes, specifically hospital admission, unscheduled healthcare visits and rescue courses of oral steroids. The most frequent therapeutic intervention was maintenance oral corticosteroids and most steroid sparing agents (apart from omalizumab) demonstrated minimal steroid sparing benefit. A significant unmet clinical need remains in this group, specifically a requirement for therapies which reduce systemic steroid exposure.

BACKGROUND

We have previously published the clinical features of a well characterised group of patients with refractory asthma from specialist UK centres operating established dedicated multidisciplinary assessment protocols and identified important differences between patient groups in individual centres.1 Using the national online registry, we have now audited clinical outcome in 349 of the 382 patients in the original cohort (median follow-up 5.1 years, IQR 1.9–5.5).

RESULTS

There were no differences in baseline demographic variables in the follow-up cohort compared with those lost to follow-up (online supplementary appendix 1). At follow-up, there was a significant improvement in lung function and a reduction in important healthcare outcomes, specifically hospital admission, unscheduled healthcare visits and rescue courses of oral steroids (table 1). These effects were generally consistent across clinical centres though unscheduled visits were significantly increased in Manchester (online supplementary appendix 2), reflecting the delivery of care at this centre where patients with an increase in symptoms are encouraged to attend the hospital centre.

There was no significant change in dose of inhaled steroid or reported reliever medication use but there was a significant increase in the number of patients prescribed maintenance oral steroids (from 146 (42%) to 199 (57%)). Only 25 patients (7%) successfully withdrew oral steroids, whereas 78 (22%) were moved onto maintenance oral steroids. There was no significant difference in the dose of oral steroids from baseline to follow-up (16.2±10.4 mg baseline, 15.3±12.8 follow-up).

Consistent with this widespread use of oral steroids, there was a significant reduction in blood eosinophils and increase in body mass index (BMI) (table 1). There was a non-significant trend for the subjects on oral steroids at follow-up to have a higher BMI compared with those not on oral steroids (subjects not on oral steroids 29.5±7.0, subjects on oral steroids 30.9±6.0, p=0.07). However, BMI also increased in patients not on maintenance steroids at follow-up (baseline BMI 28.3±6.8 vs follow-up BMI 29.2±6.9, p<0.001); in this group median rescue steroid exposure was one course of steroids in the preceding 12 months (IQR 0–5).

While blood eosinophils decreased, exhaled nitric oxide paradoxically increased. Because paired fractional exhaled nitric oxide (FeNO) data were only available in a limited number of patients, we examined paired blood eosinophil counts in this subgroup (n=75). The paradoxical fall in blood eosinophils and rise in FeNO were also apparent in this group (eosinophil count in subjects with paired FeNO measurements — baseline eosinophils × 10⁹/litre, median 0.33 (IQR 0.12–0.54) vs follow-up eosinophils, median 0.24 (IQR 0.1–0.4), p=0.001; and baseline FeNO ppb, 47 (IQR 22–69) vs follow-up FeNO, 88 (IQR 76–99), p<0.001).

Steroid sparing strategies (online supplementary appendix 3) and additional therapeutic strategies (online supplementary appendix 4) utilised in this refractory population are shown by centre; therapeutic success was defined by the treating clinician. In general, small numbers of patients were tried on steroid-sparing strategies and few were recorded as clinically beneficial. The use of other interventions was infrequent and variable across clinical centres.

Responders to omalizumab (57 of 59 (65%) based on criteria for the National Health Service Outcomes Drug Reimbursement Scheme, http://guidance.nice.org.uk/TA133/Guidance/doc/English) were more likely to be off oral steroids at clinical follow-up (17 of 57 vs 4 of 22, p=0.031, OR 3.8

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Table 1  Lung function and healthcare outcomes for cohort

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-bronchodilator FEV1 % predicted (259)</td>
<td>66.4 ± 23.7</td>
<td>72.7 ± 26.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-bronchodilator FVC % predicted (242)</td>
<td>82.7 ± 20.3</td>
<td>86.5 ± 21.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 % predicted (77)</td>
<td>79.2 ± 21.5</td>
<td>77.6 ± 30.7</td>
<td>0.61</td>
</tr>
<tr>
<td>Post-bronchodilator FVC % predicted (72)</td>
<td>90.6 ± 19.8</td>
<td>86.3 ± 25.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Rescue oral steroids in previous 12 months (302)</td>
<td>4 (2–6)</td>
<td>2 (0–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital admissions in previous 12 months (324)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Unscheduled visits in previous 12 months (315)</td>
<td>4 (2–6)</td>
<td>2 (0–6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Inhaled steroid dose, BDP equivalent (327)</td>
<td>2000 (1000–2000)</td>
<td>2000 (1200–2000)</td>
<td>0.89</td>
</tr>
<tr>
<td>Average daily SABA use (205)</td>
<td>6 (4–9)</td>
<td>8 (4–10)</td>
<td>0.058</td>
</tr>
<tr>
<td>Blood eosinophils (206)</td>
<td>0.33 (0.11–0.60)</td>
<td>0.20 (0.09–0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FeNO (112)</td>
<td>40 (18–69)</td>
<td>89 (77–102)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.2 ± 6.5</td>
<td>30.2 ± 6.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Group data (mean ± SD or median (IQR)) for all subjects are presented in column 1 followed by data for individual centres. Comparisons were made using paired samples t tests or Wilcoxon signed rank tests; significance was taken as p < 0.05.

(95% CI 1.0 to 18.2), χ²). Individual responses also support a steroid-sparing effect—in subjects on maintenance oral steroids pre omalizumab (n = 28), 9 withdrew oral steroids completely (baseline dose 20 mg (10–35 mg)), 11 had a steroid dose reduction (baseline dose 20 mg (15–20 mg), follow-up 13 mg (10–15 mg), p = 0.003, Wilcoxon signed rank test) and 8 had an increase in dose (10 mg (7–10 mg), follow-up 12.25 (10–15 mg), p = 0.027, Wilcoxon signed rank test). Of the 88 subjects whose condition responded to omalizumab only 1 progressed to oral steroids, whereas of those on omalizumab whose condition did not respond, 18 of 22 were on oral steroids at follow-up (15 mg (10–25 mg)).

Using logistic regression, baseline predictors of maintenance oral steroids at follow-up were maintenance oral steroids at baseline (OR 8.3, 95% CI 4.8 to 14.4), male gender (OR 2.2, 95% CI 1.3 to 3.7), and rescue steroids in the preceding year (OR 8.3, 95% CI 4.8 to 14.4), male gender (OR 2.2, 95% CI 1.3 to 3.7), and rescue steroids in the preceding year (OR 8.3, 95% CI 4.8 to 14.4), and rescue steroids in the preceding year (OR 8.3, 95% CI 4.8 to 14.4). The only additional therapeutic intervention that demonstrated a steroid-sparing effect was omalizumab. In subjects who received a clinical trial of omalizumab, the overall response rate was 65% and 20 (71%) of the 28 on oral steroids either withdrew or significantly reduced their oral steroid dose.

In summary, this audit demonstrates improved outcomes with reduced exacerbation rates and healthcare utilisation, but at the cost of increased numbers of subjects on systemic steroids.
Steroid-sparing therapies are infrequently used and are only modestly successful in routine clinical practice. In patients who respond to omalizumab, there is the suggestion of a significant steroid-sparing effect in some but not all subjects. There remains a significant unmet clinical need in this group and specifically a requirement for therapies which reduce systemic steroid exposure.

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Contributors LGH is the coordinator of the British Thoracic Society Difficult Asthma Registry and with JS collated and managed the data for this manuscript. CEB and AM-G and RN co-lead the British Thoracic Society Difficult Asthma Network and all have contributed equally to this manuscript.

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Competing interests Ms Sweeney is supported by HSC R&D (NI) and GlaxoSmithKline (PhD studentship funding). Professor Brightling is supported by a Wellcome Senior Clinical Fellowship and has received consultancy fees and or research funding from GlaxoSmithKline, AZ, MedImmune, Amgen, Novartis, Chiesi, BI and Roche. Dr Menzies-Gow has attended advisory boards for Novartis and Genentech. He has received sponsorship to attend international meetings from GlaxoSmithKline, AZ, MedImmune, Amgen, Novartis, Chiesi and Roche. Dr Niven has sat on advisory boards for the following companies in the last 3 years: Astra Zeneca, GlaxoSmithKline, Novartis and Medimmune. Sweeney is supported by HSC R&D (NI) and GlaxoSmithKline (PhD studentship funding). Professor Heaney has attended advisory boards for Novartis and Genentech, and GlaxoSmithKline, has taken part in Advisory Boards and given lectures at meetings supported by GlaxoSmithKline, Merck Sharpe & Dohme, Nycomed, Novartis and Astra Zeneca. He has received support funding to attend International Respiratory meetings (Astra Zeneca, Chiesi, Novartis, Teva and GlaxoSmithKline) and has taken part in asthma clinical trials (GSK and Genentech) for which his Institution was remunerated. None of these activities have any direct relationship to the content of this manuscript.

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