AUDIT UPDATE

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

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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 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 582 patients in the original cohort (median follow-up 3.1 years, IQR 1.9–6.9). Dose of oral steroids from baseline to follow-up (17 of 37 vs 4 of 22, p<0.031, OR 3.86, 95% CI 1.46 to 10.0), and increase in body mass index (BMI) (apart from omalizumab) were apparent in this group (follow-up BMI 29.2 vs baseline BMI 26.8, p<0.001; in 25 patients (42%) at baseline vs 199 (57%) at follow-up). 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 mg 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 (37 of 59 (63%) 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=0.081, OR 3.8

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Post-bronchodilator FEV1 %

steroids (with 115 of 222 women (52%) were on maintenance oral
95% CI 1.1 to 4.9). At follow-up, 84 of 127 men (66%) compared
baseline (OR 8.3, 95% CI 4.8 to 14.4), male gender (OR 2.2, 95%
oral steroids at follow-up were maintenance oral steroids at
previous 12 months (315)

Unscheduled visits in
Hospital admissions in
Predicted (72)
Pre-bronchodilator FVC %

pre omalizumab (n
10
20 mg, follow-up 13 mg
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 other 8 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 1.5 to 5.7), and rescue steroids in the preceding year (OR 2.3,
95% CI 1.1 to 4.9). At follow-up, 84 of 127 men (66%) compared
with 115 of 222 women (52%) were on maintenance oral
steroids (χ²; p<0.01).

**DISCUSSION**

This audit provides the first outcome data on a well charac-
terised cohort of adults with severe refractory asthma. We report
significant changes in important healthcare outcomes, particu-
larly reductions in unscheduled visits, hospital admissions and
rescue oral steroids, which taken collectively suggests a reduc-
tion in severe exacerbations. Improvement was also seen in lung
function, but notably daily reliever medication use was not
different, suggesting persistent symptomatic morbidity in this
group. Because of the precise characterisation of this group, we
believe this is due to asthma and not other non-asthma
comorbidities.

As this is an observational clinical registry, we cannot exclude
the possibility that the improvement in healthcare outcomes
simply represents ‘regression to the mean’, since at the time of
referral and initial assessment, patients are likely to be clinically
unwell. However, 60–75% of patients in these centres are
tertiary referrals and had difficult asthma for prolonged periods
prior to assessment, making regression to the mean unlikely to
be the entire explanation for the observed improvement. Even at
baseline, in this severe asthmatic population, hospital admission
rate was relatively low, but unscheduled healthcare contact and
rescue steroid courses were high. With appropriate specialist
management, hospital admission rates were further reduced,
suggesting the economic cost of refractory asthma is unlikely to
be driven by hospital admission.

The commonest therapeutic strategy was initiation of main-
tenance steroids, which is consistent with the reduction in
peripheral blood eosinophils and the reduction in rescue oral
steroid courses. The dissociation between FeNO, clinical
outcome and blood eosinophilia is consistent with other data,
which have shown that FeNO-based strategies have not been
able to reduce exacerbation rates. In a recent oral steroid
tapering study, which included FeNO as part of the steroid
reduction algorithm, weekly Asthma Control Questionnaire and
forced expiratory volume in 1 s measurement were the major
drivers of steroid reduction, with minimal contribution from
daily FeNO. Collectively, these data question whether FeNO is
useful in adjusting steroid dose in patients on maintenance or
frequent bursts of oral steroids.

The increase in BMI is also consistent with more steroid
exposure, but BMI also increased in subjects not on maintenance
oral steroids at follow-up. This latter group remained on high-
dose inhaled steroids but rescue steroid exposure in the
preceding 12 months was relatively low (median 1, IQR 0–5),
suggesting that BMI increase is not exclusively related to oral
steroid exposure in this population, and reduced exercise
capacity due to persistent asthma may be relevant.

The best predictor of being on oral steroids was being on them
at referral, which might initially suggest that specialist services
have a minimal effect on maintenance steroid exposure in this
patient population. However, this cohort of patients had well
phenotyped refractory asthma after detailed systematic evalua-
tion and issues such as incorrect diagnosis, comorbidities and
non-adherence have been identified and these subjects excluded.
One of the major advantages and benefits of a specialist difficult
asthma service is ensuring precise patient characterisation and
appropriateness of high-dose asthma therapy in subjects with
refractory asthma.

It is unclear why a greater proportion of men were more likely
to be on oral steroids at follow-up. Cohorts of difficult and
refractory asthma typically include more women, but these
data suggest that the requirement for oral steroids, which might
be interpreted as one index of severity, is less common in
women. Frequency of rescue steroids is also predictive of
progression as this identifies someone with steroid-responsive
disease prone to exacerbation despite high-dose inhaled therapy.
Steroid-sparing strategies (cyclosporin, methotrexate, azathio-
prine, mycophenolate) are used variably across centres, with
limited clinical success. The low trial rate in some centres re-
mits a steroid-sparing effect was omalizumab. In subjects
who received a clinical trial of omalizumab, the overall response
rate was 63% 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.
Chest clinic

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, Novartis and Boeringer Ingelheim. He has received lecture fees from Novartis, GlaxoSmithKline, Astra Zeneca and Chiesi. Dr Niven has received an unrestricted grant of £10 000 from Novartis in 2010 towards development of clinical services at the University Hospital of South Manchester. In addition he has lectured in the field of severe allergic asthma at Novartis-sponsored meetings receiving honoraria in total not exceeding £5000 in the last 3 years. Dr Niven has also performed lecturing at pharmaceutically sponsored meetings for the following pharmaceutical companies in the last 3 years: Vectura, Novartis, GlaxoSmithKline, receiving reimbursement not exceeding £1000. He has received sponsorship support to attend international academic meetings. Dr Niven (or any members of his family) has no shares or any percuriary interest in any pharmaceutical industry and has nothing to gain financially from the publication of this paper. Dr C Patterson’s spouse holds shares in GlaxoSmithKline. Professor Heaney has received grant funding from 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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