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Severe asthma treatment: need for characterising patients

Liam G Heaney, Douglas S Robinson

**Context** Asthma is readily diagnosed in most cases and usually responds to inhaled corticosteroids with or without long-acting β agonists, theophyllines, or leukotriene-receptor antagonists, adjusted stepwise according to symptoms and lung function. However, up to 40% of adult patients with asthma remain symptomatic, and up to 5% have difficult-to-control asthma despite multiple therapies. It is suggested that higher doses of inhaled steroids with long-acting β agonists should be used for total control of symptoms; and anti-IgE therapy is newly licensed in the USA. However, difficult-to-control asthma is complex and multifactorial, and is often due to severe or therapy-resistant asthma.

**Starting point** Last year saw encouraging reports on omalizumab (anti-IgE therapy) in severe allergic asthma, by Stephen Holgate, Jon Ayres, and their respective colleagues (Clin Exp Allergy 2004; 34: 632–38; Allergy 2004; 59: 701–08). Omalizumab reduced exacerbation rates, improved asthma symptoms and quality of life, and allowed lower doses of inhaled steroid compared with placebo. In placebo-controlled studies with anti-IgE, many patients were able to substantially reduce and even withdraw inhaled steroids in the placebo arm.

**Where next** Severe asthma is often defined as persisting symptoms despite high-dose inhaled steroids. This definition is likely to include patients with various reasons for their persisting symptoms, for whom additional treatment is not always required. Before starting new therapy, it is important to systematically evaluate asthmatic patients to accurately define their disease and to identify those whose symptoms are caused by other factors, and thus avoid unnecessary medication. There might also be subgroups that have differing underlying inflammatory processes and who will respond differently to individual treatments.

Last year saw reports on the effect of omalizumab (anti-IgE therapy) in severe allergic asthma.12 The licensing of this agent in the USA has had an impact on severe disease. These results add to other studies3–5 (table) supporting an add-on benefit of omalizumab compared with placebo, with reduction in inhaled-steroid dose and fewer exacerbations requiring oral corticosteroids.

A major endpoint for most of the omalizumab studies was reduction in inhaled-steroid dose. Meta-analysis suggested a reduction of about 100 μg a day over that achieved in placebo-randomised patients.3 Exacerbation rates and symptom scores were also reduced but without overall changes in lung function in most studies.4 In controlled trials of omalizumab in moderate-to-severe asthma,1,4 inhaled-steroid dose could also be reduced in many patients on placebo and other proven add-on therapies were often not used (eg, under half were taking long-acting β2 agonists5). These results raise the issues of how to select patients, how response is to be assessed, and whether the cost of treatment (more than US$10 000 a year) is justified. Other immunotherapies, such as antibodies to tumour necrosis factor α, might prove useful in asthma,7 and as expensive and complex therapies become available, it will be important to carefully identify which patients will benefit and target therapy appropriately.

**Definition of severe asthma**

Defining asthma severity on the basis of persisting symptoms despite high-dose inhaled steroids is problematic, and systematic evaluations of difficult-to-manage asthma give insight into the role of different factors in this population.8,9 A universal definition of severe asthma is difficult because of different patterns of disease. For example, frequent severe exacerbations on the background of relatively normal lung function (type 2 brittle asthma10) would be defined by most as severe but might not fit a definition based on a single assessment. There are workshop definitions of difficult-to-treat asthma,11,12 similar to the following study outcomes.

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean inhaled steroid dose at study entry (μg)</th>
<th>Patients (%) reducing inhaled-steroid dose by ≥50% inhaled steroids</th>
<th>Number (%) withdrawing</th>
<th>Exacerbations during steroid reduction (mean per patient)</th>
<th>Other major outcomes (compared with placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Anti-IgE</td>
<td>Placebo</td>
<td>Anti-IgE</td>
<td>Placebo</td>
</tr>
<tr>
<td>Holgate et al11</td>
<td>1362.5</td>
<td>1375.0</td>
<td>51</td>
<td>74*</td>
<td>10</td>
</tr>
<tr>
<td>Saler et al12</td>
<td>772.1</td>
<td>769.0</td>
<td>55</td>
<td>79</td>
<td>19</td>
</tr>
<tr>
<td>Busse et al13</td>
<td>568</td>
<td>570</td>
<td>55</td>
<td>72†</td>
<td>19</td>
</tr>
</tbody>
</table>

*p<0.001, †p<0.001, ‡p=0.003.

| Table: Placebo-controlled trials in moderate-to-severe allergic asthma |

Lancet 2005; 365: 974–76

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**Rapid Review**
those used in two recent series. The American Thoracic Society suggested major and minor diagnostic criteria for refractory asthma. The patient should have mild-to-moderate symptoms despite treatment requiring continuous or near-continuous oral corticosteroids or high-dose inhaled steroids (equivalent to at least 1000 µg fluticasone propionate a day). Also, the patient should have two of: requirement for additional long-acting β, agonist, theophylline, or leukotriene-receptor antagonist, symptoms requiring daily or near daily use of short-acting β agonists, persistent airflow obstruction (<80% of predicted forced expiratory volume in 1 s), one or more urgent-care visits a year, three or more oral-steroid bursts a year, prompt deterioration on reducing inhaled-steroid dose, or a near-fatal past asthma event. This definition requires that other conditions have been excluded, exacerbating factors treated, and the patient is generally adherent.

**Other diagnoses and exacerbating factors**

Several conditions that cause respiratory symptoms might co-exist in asthmatic patients, leading to an apparent failure to respond to therapy. In both systematic evaluations, additional or alternative diagnoses were revealed in just over a third of cases (figure). There are several other additional or co-existent conditions that might make asthma difficult to control: smoking and chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis, bronchiectasis, chronic infection (including chlamydia), rhinosinusitis, vocal-cord dysfunction, gastro-oesophageal reflux, allergen or occupational exposure, aspirin, systemic disease (eg, thyroid disease, vasculitis), psychological factors, poor adherence, and socioeconomic factors. Dysfunctional breathlessness seems prevalent in all grades of asthma, and in a small series of patients previously designated as having steroid-resistant asthma, when properly evaluated, seven of 14 had evidence of hyperventilation. Identification and management of the condition causing the symptoms, rather than more asthma therapy, is a more appropriate strategy.

Although asthma might remain difficult to control if unidentified exacerbating factors persist, there is little evidence that treating such factors has much effect on asthma control. Inhaled allergens might be important in driving asthmatic inflammation, although success with allergen-avoidance strategies has yet to be convincingly shown. Occupational exposure is amenable to intervention, but was not a major problem in either cohort (most patients were not working because of symptom severity). Asthma may be exacerbated by ingestion of certain drugs (eg, non-steroidal anti-inflammatory drugs and β blockers). Gastro-oesophageal reflux often occurs with asthma but evidence that treatment of reflux affects asthma control is lacking; treatment was not associated with better asthma outcome in the Belfast cohort. Rhinosinusitis is common in difficult-to-treat asthma, but again management did not relate to asthma outcome.

**Poor adherence and psychological factors**

One of the commonest reasons for a poor response to asthma therapy is not taking medication. The Brompton study assessed adherence in those on oral prednisolone: half had low or undetectable serum prednisolone and/or normal cortisol, suggesting non-adherence. In the Belfast cohort, of 44 patients taking theophylline and 14 of 25 taking prednisolone had unrecordable serum levels of drug. Non-adherence with steroid therapy in this population must be assessed when defining “steroid-resistant” or “(systemic) steroid-dependent” asthma. Non-adherence also has major implications when reduction in steroid therapy is an outcome, because rigorous assessment of adherence is required. Assessing non-adherence with inhaled therapy is difficult, and issues that might lead to poor adherence must be addressed at each clinic visit.

Reasons for poor adherence include lack of immediate benefit from anti-inflammatory therapy, side-effect fears, resentment about the need for therapy, poor education, economic restriction on access to health care, demographic factors such as sex and ethnicity, and secondary gain. Adherence should be better with omalizumab, because this drug is injected subcutaneously (fortnightly or monthly; home therapy would raise issues of adherence). But it seems difficult to justify omalizumab for asthma if other prescribed therapy is not being taken; directly observed therapy or injected depot-steroids might be more appropriate. Education and self-management plans work, and are recommended in most guidelines. A written management plan, careful follow-up, and addressing non-adherence might be more cost effective than injected bioengineered therapy in some patients.

It is hard to separate whether having difficult-to-treat or life-threatening asthma makes patients psychologically unstable, or whether psychiatric morbidity worsens asthma control. Psychosocial morbidity is associated with asthma death and near-fatal asthma in most but not all studies. In the Belfast cohort, of 65 (49%) sequential patients had a psychiatric diagnosis, mainly depression, although
identification and appropriate management was not associated with better asthma outcome. In the Brompton cohort,3 33 of 88 (38%) patients had a psychiatric component to their asthma. However, whether psychological factors are causally linked with asthma severity or whether management of identified psychiatric morbidity can affect asthma outcome remains unclear.

Therapy-resistant asthma
Therapy-resistant asthma has been defined as persisting symptoms due to asthma despite high-dose inhaled steroids (2000 µg beclomethasone dipropionate or equivalent) plus long-acting β₂ agonist, with the requirement for either maintenance systemic steroids or at least two rescue courses of steroids over 12 months and despite trials of add-ons such as a leukotriene-receptor antagonist or theophylline.4 These are the patients for whom omalizumab might be appropriate.

Key to this definition is that persisting symptoms are due to asthma, and other mechanisms and poor adherence have been excluded. Addressing these issues with systematic evaluation and management resulted in half the patients with difficult-to-treat asthma in the Brompton study being stabilised with reduced treatment requirements.5 In the Brompton cohort, 34% of the patients with difficult-to-control asthma had alternative mechanisms for persisting symptoms.6 Also, almost a third of the Brompton patients had fixed airflow obstruction; whether this form of asthma is amenable to novel interventions such as anti-IgE therapy will be important to define.

Although further studies are required, there are different characteristics of severe asthma that might require alternative differing treatment strategies. Non-invasive monitoring of inflammation can be used to guide therapy and reduce exacerbation rates in asthma.7 Whether such measures can identify subgroups, such as those with persistent eosinophilic inflammation who might respond to anti-interleukin-5 therapy (most patients do not)8 remains to be seen. Understanding the underlying mechanisms of refractory asthma is a future priority.

Conclusion
Omalizumab holds great promise for difficult-to-control asthma. However, before using expensive new therapies, patients with difficult-to-manage asthma should be systematically characterised so that new treatments are appropriately targeted.

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