Chapter 21

Management of difficult-to-treat severe asthma

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Summary

Severe asthma remains a frustrating condition for both the patient and the clinician. Significant advances have been made over the last decade and there is now a consensus for these patients to receive a thorough systematic assessment to ensure that asthma is the correct diagnosis, that patients adhere to their prescribed therapies and that any comorbidities are treated.

Several cohorts of patients with severe asthma have been published. They have clearly demonstrated that severe asthma is a heterogeneous condition comprising of several different phenotypes. This heterogeneity, to a certain extent, explains the failure of any one medication to be effective for the whole severe asthma population.

When examining the treatment options, it is apparent that there is little evidence to guide the clinician. The majority of clinical trials have been carried out in milder asthmatics and the results extrapolated to the more severe population. The hope for the next decade lies with identifying all the relevant phenotypes of severe asthma to allow effective targeted therapy for the individual patient.

Keywords: Severe asthma, severe asthma phenotypes, systematic assessment

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Eur Respir Mon 2011. 51, 282–296.

European Respiratory Monograph;
ISSN: 1025-448x.
DOI: 10.1183/1025448x.10002610

A decade ago the American Thoracic Society (ATS) [1] workshop on refractory asthma and the European Respiratory Society (ERS) Task Force on severe asthma [2] both concluded that these conditions were poorly understood and often frustrating to treat since this particular category of patients appeared to be refractory to the available treatments. This statement still has resonance despite significant attempts to improve the understanding of severe asthma over the last decade, nevertheless progress is being achieved. At a minimum, the adoption of asthma guidelines has meant that the management of mild-to-moderate asthma is now well established and inhaled combination therapy with a long-acting β-agonist (LABA) and an inhaled corticosteroid (ICS) is effective treatment for most patients. This has also led to the recognition that a proportion of

patients with asthma do not achieve adequate and acceptable control of asthma with this combination therapy. Recent guidelines also recognise that these patients still remain uncontrolled, despite the addition of other controllers, namely leukotriene receptor antagonists, theophyllines and, in some, the use of bursts or continuous oral corticosteroids (OCS).

Several terms are commonly used to denote severe asthma including difficult asthma, therapy-resistant asthma, brittle asthma and severe refractory disease, all of which reflect the different aspects of this condition that require treatment at Step4 or Step 5 of the guidelines. Patients with difficult asthma, after a systematic assessment, are either confirmed as having severe asthma or given an alternative and or additional diagnosis, including nonadherence.

Difficulties associated with managing severe asthma

Severe asthma is a syndrome that is likely to comprise many different phenotypes which, at present, are arbitrarily divided into groups depending on age of onset, presence of atopy, nature of airway inflammation and lung physiology. Whilst splitting patients along these lines has some merit it has not yet led to many real advances for the individual patient, with the notable exception of anti-immunoglobulin (Ig)E therapy for severe allergic asthma. The challenge over the next 10 years is to improve the current understanding with regards the different phenotypes in order to revolutionise patient care with targeted therapies, and thereby improve the prevention of exacerbations and lung function decline with time. This means that patients with severe asthma need to be assessed systematically over a prolonged period of time, *i.e.* 6–12 months. In this way patients can be observed with regards to their adherence to therapy, the diagnosis of their asthma can be established, their treatments maximised and their clinical phenotype determined. Perhaps the greatest difficulty in the management of this patient group is the lack of new effective specific therapies, such that best outcome currently rests with the judicious use of currently available therapies.

Systematic approach to difficult-to-treat asthma

A systematic approach to the management of patients referred with difficult-to-treat asthma is needed. In difficult-to-treat asthma patients it is necessary to ascertain that the diagnosis is indeed asthma and that the condition is being correctly and adequately treated. It is also extremely important to ensure that patients adhere to their prescribed therapies and are able to use their inhaler devices correctly. Conditions that may mimic asthma are listed in table 1. The second part of this approach to management is to ascertain if there are any comorbidities associated with asthma that may or may not contribute to increasing the asthma severity or to the loss of asthma control. Finally, the third part of management is to determine the treatments needed to achieve a better control of the asthma. For this part of the management it is necessary to observe the pattern of disease over a period of time and determine whether the patient fits into a recognised asthma phenotype. Overall this approach to severe asthma means that patients are best managed in units that have a special interest in difficult-to-treat asthma. This process of diagnosis and evaluation is likely to be completed within a 3–6-month period by several outpatient visits with or without in-patient admission for investigations, or for treatment of exacerbations, or for worsening disease. At the unit at the Royal Brompton and Harefield NHS Foundation Trust hospital (London, UK) there is a 3–4-day planned admission procedure that allows for the investigation and observation of such patients, the list of investigations is shown in table 2.

Protocol for difficult asthma

There is no gold standard concerning the systematic assessment protocol for difficult asthma, and there are no studies available to compare outcomes from different centres. At the Royal Brompton and Harefield NHS Trust hospital a multi-disciplinary approach is taken. Patients are initially reviewed by a respiratory consultant who has a specialist interest in severe asthma. They are then

Table 1. Diagnoses that may masquerade as difficult or therapy-resistant asthma

In children
Obliterative bronchiolitis
Vocal cord dysfunction
Bronchomalacia
Inhaled foreign bodies
Cystic fibrosis
Recent aspiration
Developmental abnormalities of the upper airway
Immunoglobulin deficiencies
Primary ciliary dyskinesia
In adults
Cystic fibrosis
Bronchiectasis
Inhaled foreign body
Tracheobronchomalacia
Recurrent aspiration
Chronic obstructive pulmonary disease
Congestive cardiac failure
Tumours in or impinging on central airways
Obstructive bronchiolitis
Vocal cord dysfunction
Bronchial amyloidosis
As part of the asthmatic diathesis
Allergic bronchopulmonary aspergillosis
Pulmonary eosinophilic syndromes, *e.g.* Churg–Strauss syndrome

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admitted for a programmed set of investigations that include: skin-prick testing for 10 common aeroallergens; full pulmonary function tests and bronchodilator reversibility; high-resolution computed tomography (HRCT) of the thorax; ear, nose and throat (ENT) review; and analysis of induced sputum. Blood samples are sent for laboratory testing to exclude immune deficiency, Aspergillus lung disease and Churg–Strauss syndrome. Adherence is assessed by measuring serum prednisolone and cortisol levels 2 hours after ingestion and theophylline levels 4–6 hours post-ingestion. Additional tests that may be requested on an individual patient basis include bone densitometry, CT of sinuses, oesophageal pH monitoring, histamine PC_{20} (provocative concentration causing a 20% fall in forced expiratory volume in 1 second (FEV_1)) and relevant cardiac investigations. The patients are also seen by a respiratory physiotherapist, health psychologist, psychiatrist and allergist as required. The patient's history is recorded with a proforma designed to document all the relevant information including occupational exposures, pet exposure, indoor allergens and seasonal allergens. A sleep history is taken along with the Epworth Sleepiness Score (ESS) and, if required, patients are investigated for sleep-disordered breathing. Patients are also referred to the smoking cessation clinic if necessary. Patients are reviewed by a dedicated specialist severe asthma nurse to ensure that their inhaler technique is optimal and that they are using the correct device for them. Their asthma management plan is also assessed to ensure that it is at an optimum. At the end of a patient's admission the results are discussed by the multidisciplinary team and reviewed by their consultant with a clear diagnosis and management plan in place.

Whilst it is important for specialists in tertiary centres to extol the virtues of systematic assessment, of more relevance is what is actually happening outside tertiary centres for the majority of patients with difficult asthma. ROBERTS *et al.* [3] attempted to assess this by sending a postal survey to 683 consultant members of the British Thoracic Society (BTS) which was designed to elicit respondents' views on how they would manage four clinical scenarios and what resources they had available to them. There was a 50.4% response rate of which 21 consultants reported a special interest in difficult asthma. It was found that the total number of patients with difficult asthma under the care of 280 consultants was 7,027, with 3,635 of these under the care of 21 specialists. Only 22.7% had access to a specific clinic for patients with difficult asthma. The responses of the 21 specialists were compared with the 152 general respiratory consultants. Specialists were more likely to have access to skin-prick tests, liaison psychiatry and prednisolone and cortisol assays. Overall, slightly more than 20% of patients got referred to the ENT team and 40% underwent HRCT of their thorax. The specialists were each caring for a mean of 173 patients with difficult asthma. However, the investigations available to the specialists were below what would be expected

of a systematic assessment. Only 25% would routinely send prednisolone and cortisol assays, and 14% would not routinely perform skin-prick tests for the common aeroallergens. Alarmingly, the most common misdiagnosis for difficult asthma reported by the respondents was psychiatric disease. Clearly, significant education within the general respiratory community and resource allocation is still required before all patients with difficult asthma undergo a systematic assessment at a dedicated centre.

Table 2. Investigations used in systematic assessment for severe asthma at the Royal Brompton and Harefield NHS Foundation Trust hospital (London, UK)

Blood test
Eosinophil count
IgE
RAST to aeroallergens including, *Aspergillus fumigatus*
Aspergillus IgG
ANCA
Total Ig and response to specific vaccination
Prednisolone and cortisol levels
Theophylline levels
Skin prick tests to 10 common aeroallergens
Pulmonary function tests
Spirometry with bronchodilator reversibility
Lung volumes
Gas transfer
Histamine PC_{20}
Imaging
CXR
HRCT thorax
CT sinuses if indicated
MDT review as required
ENT
Clinical nurse specialist
Physiotherapy
Health psychology
Allergy
Dietician
Psychiatry
Measurement of airway inflammation
Induced sputum eosinophil count
Exhaled nitric oxide
Other investigations as required
Bone density
Oesophageal pH monitoring
Sleep study
Echocardiogram

Ig: immunoglobulin; RAST: radioallergosorbent test; ANCA: anti-neutrophil cytoplasmic antibodies; PC_{20}: provocative concentration causing a 20% fall in forced expiratory volume in 1 second; CXR: chest radiograph; HRCT: high-resolution computed tomography (CT); MDT: multidisciplinary team; ENT: ear, nose and throat.

ROBINSON *et al.* [4] have reported their experience of the first 100 patients that underwent their difficult asthma protocol [4]. After systematic review, 12 patients were found to have nonasthma diagnosis, including chronic obstructive pulmonary disease (COPD; n=6), α_1-antitrypsin deficiency, cystic fibrosis and cardiomyopathy. In a further seven patients, a diagnosis of respiratory disease coexistent with asthma was made, the most common of which was bronchiectasis (n=3). Of the remaining patients, 55 had an asthma diagnosis confirmed by the demonstration of significant reversible airflow narrowing or increased diurnal peak flow variability, whilst 20 did not show either. Nonadherence with prednisolone was assessed using serum prednisolone and cortisol levels. In nine out of the 18 patients who were prescribed >15 mg·day^{-1} of prednisolone in the confirmed asthma group, morning prednisone levels were undetectable leading to a presumptive diagnosis of nonadherence. A major psychiatric component was detected in 10 patients. This study clearly demonstrated the value of systematic evaluation as it identified that 32% of patients have another or additional respiratory disease and other patients have psychiatric comorbidity or poor adherence with prescribed therapy.

HEANEY *et al.* [5] also reported on a similar protocol where all patients were followed up for a minimum of 12 months for assessment. Following a systematic assessment and management of any identified alternative diagnoses or comorbidities, 39 of the 73 patients had good symptom control and 34 were considered to have therapy-resistant asthma (TRA). The recorded period of instability was significantly longer in subjects who subsequently had TRA. They also tended to be on a higher dose of inhaled steroid at referral, had significantly more courses of systemic steroids

in the previous year and were more likely to be on maintenance systemic steroids at referral. 34% had an additional diagnosis including bronchiectasis and dysfunctional breathlessness. It was found that gastro-oesophageal reflux, ENT pathology and psychiatric morbidity were common, but were not more prevalent in either group, although subjects with TRA were more likely to have osteoporosis. After evaluation and management, subjects with TRA were on significantly higher doses of inhaled steroids and also had a significantly lower best FEV_1 recorded during the follow-up period. Using multivariate logistic regression analysis, an inhaled steroid dose $>$2,000 μg of beclomethasone dipropionate (BDP), previous assessment by a respiratory specialist and an initial $FEV_1<70\%$ at referral resulted in the prediction at final diagnosis of TRA.

Characteristics of severe asthma from multicentre studies

Several multicentre cohorts of severe asthma have now been published and a review of these is informative in guiding us towards the correct management of severe asthma.

European Network for Understanding Mechanisms Of Severe Asthma (ENFUMOSA)

A total of 163 subjects with severe asthma from 12 centres in nine European countries were compared with 158 subjects whose asthma was controlled by low doses of ICS (median dose of BDP 666 μg) termed mild asthma [6]. There was no difference in terms of age between the severe and mild asthma groups; however, females dominated the severe group (4.4:1 *versus* 1.6:1, respictively). Females with severe disease also had a higher body mass index (BMI). Both the serum total IgE and the skin-prick test positivity were lower in the severe group. In a multiple linear regression analysis the following were independently associated with severe asthma: female sex, perennial symptoms and exacerbations during the autumn. Patients with severe asthma had a lower baseline FEV_1 with more obstructive spirometry and evidence of gas trapping. They also had a marginally reduced transfer coefficient of the lung for carbon monoxide (K_{CO}) and were slightly hypoxic and hypocapnic at rest. These findings suggest that there is a component of fixed and small airways disease in severe asthma. Those with severe disease had a significantly greater sputum neutrophilia, but no increase in sputum eosinophils. Patients with severe asthma treated with OCS had almost a three-fold higher level of exhaled nitric oxide than those treated only with ICS. The persistence of eosinophils in the sputum in combination with the elevated exhaled nitric oxide suggests that severe asthma might be characterised by diminished or suboptimal sensitivity to corticosteroids. A potential risk factor that emerged from the ENFUMOSA study was exposure to aspirin. Aspirin intake was a self-reported trigger with an OR of 5.12 for severe disease in females and an odds ratio (OR) of 4.61 in males.

The Epidemiology and Natural history of Asthma Outcomes and treatment Regimes (TENOR) study

The strength of TENOR lies in its size: 283 study sites recruiting 4,756 patients [7]. TENOR was a prospective, observational, multicentre, 3-year study (2001–2004) of patients in the USA who had been diagnosed as having severe or difficult-to-treat asthma. According to physician evaluation 48% had severe asthma. Due to its unique nature TENOR has provided many insights into the natural history of severe asthma and its size allows important patterns to emerge. For instance, despite there being an overall increase in mean IgE levels in patients with severe asthma compared with mild and moderate asthma, the investigators demonstrated that IgE increased with asthma severity in children and adolescents but no such relationship existed in adults.

Severe Asthma Research Programme

The Severe Asthma Research Program (SARP) is a very well characterised cohort of severe asthmatics consisting of 204 patients who were recruited from nine US sites and one UK site [8].

These severe asthma subjects were compared with 70 patients with moderate asthma and 164 subjects with mild asthma. Subjects with severe asthma were older with a longer duration of the disease. The frequency of all reported symptoms increased with disease severity. Urgent healthcare utilisation was also more common and more frequent in severe asthma subjects. As with previous studies, patients with severe asthma were less atopic with a lower FEV_1 and had reduced bronchodilator reversibility, suggesting that these patients are a different phenotype rather than just being at the severe end of the spectrum of a single phenotype. Exhaled nitric oxide levels did not differentiate the mild, moderate and severe groups, with a wide range of values within each group. Aspirin sensitivity, gastro-oesophageal reflux and a history of sinopulmonary infections were reported more frequently in the severe group. Following univariate analysis it was observed that five variables independently increased the likelihood that a subject would be classified with severe asthma: pre-bronchodilator FEV_1% predicted with a 36% increase in risk of being classified as severe asthma for every 5% fall in FEV_1; history of pneumonia; lower numbers of blood basophils; asthma symptoms during routine physical activities; and lower numbers of positive skin-prick test reactions to the common aeroallergens. The cohort was subdivided into early onset ($<$12 years old) and late onset ($\geq$12 years old) asthma. Pulmonary function was lower in late onset asthmatics, despite the shorter duration of the disease and was associated with less bronchial hyperresponsiveness. Subjects with early onset asthma had more positive skin-prick tests and an increased number of allergy triggers. More subjects with late onset asthma reported a history of sinus infection and pneumonia.

Cluster analysis has recently been applied to the SARP cohort to identify novel asthma phenotypes [9]. Five distinct groups have been identified and referred to here as clusters. 15% are grouped into cluster one characterised by younger, predominantly female subjects, with early onset atopic asthma and normal lung function treated with two or fewer controller medications (82%) and minimal healthcare utilisation. Cluster two was the largest group (44%) consisting of slightly older subjects, two thirds of whom were female, with early onset atopic asthma and preserved lung function but increased medication requirements and healthcare utilisation. Cluster three was the smallest group (8%) consisting of mostly older obese females with late-onset nonatopic asthma, moderate reductions in FEV_1 (71%, $<$80% pred) and frequent OCS use to manage exacerbations. The remaining 33% were grouped into clusters four and five. In cluster four the male to female ratio was equal with primarily early onset atopic disease. There were more females (63%) in cluster five with mainly late onset disease (69%) and less atopy. Subjects in cluster four had a mean FEV_1 of 57% pred with 40% able to reverse to $>$80%. The mean FEV_1 in cluster five was 43% pred with 94% remaining at $<$80% after bronchodilators. Subjects in cluster 5 were treated more frequently with systemic corticosteroids (47%) than cluster 4 (39%). In general comorbidities tracked with increasing severity and age of the clusters.

Blood eosinophils and exhaled nitric oxide levels were similar in all clusters. Serum IgE was highest in the atopic clusters and methacholine hyperresponsiveness was highest in clusters four and five. Sputum eosinophils were elevated in clusters three, four and five and neutrophils were highest in cluster five. These five clusters support the concept that asthma is a heterogeneous condition. The divergent phenotypes suggest different pathophysiology in asthma for the different severities, which may determine the response to treatment and therefore asthma control.

BTS difficult asthma network patient cohort

This registry comprised of cross sectional data for 382 patients with severe asthma from four clinical centres in the UK [10]. Many of the demographic variables including sex, ethnicity and smoking prevalence were similar in UK centres. However, other factors including atopy prevalence, family history, lung function, emergency healthcare utilisation and medication burden were different from the previously published cohorts. More importantly there were significant differences in several of these variables between different centres. General linear modelling with unscheduled healthcare visits, rescue oral steroids and hospital admissions as dependent variables all identified a significant association with a clinical centre. These findings are extremely important

as the previously published studies have always relied on pooling data from multiple different research centres, which may then miss important differences and confound attempts at logical phenotyping of this population.

Other cohorts

In the single centre cohort of by TEN BRINKE *et al.* [11] in Leiden (the Netherlands), two common phenotypic presentations of severe asthma have been observed: persistent airflow obstruction and recurrent exacerbators. Thus in their adult cohorts, it was shown that persistent airflow obstruction was associated with adult onset disease and longer duration of asthma, airway hyperresponsiveness and sputum eosinophilia. Similarly in the Royal Brompton and Harefield NHS Foundation Trust Hospital cohort BUMBACEA *et al.* [12] showed that a more severe degree of persistent airflow obstruction was associated with longer duration of disease, elevated exhaled nitric oxide levels and greater abnormalities detectable on an HRCT scan of the lungs. Frequent exacerbations are an important part of the severe asthma diathesis, as this is likely to be the variable that has the greatest effect on asthma control. A history of recent severe asthma exacerbations is a predictor of future severe exacerbations [13]. In the Leiden cohort, the comorbid factors associated with frequent exacerbations were severe nasal sinus disease and psychological dysfunction, in addition to recurrent respiratory infections, gastro-oesophageal reflux and obstructive sleep apnoea (OSA) [14].

Current treatments for severe asthma

In the Global Initiative for Asthma (GINA) treatment steps, patients with severe asthma are at Step 4 or Step 5, requiring a high dose of ICS with or without OCS and the addition of other controller medications including LABAs, leukotriene modifiers and theophyllines (fig. 1).

The use of ICS or OCS in severe asthma has been discussed by CHUNG *et al.* [15] previously in this Monograph. The dose of ICS needs to be increased above the usual recommended dose, at least for a trial period, as some patients may not have reached the plateau of the dose–response effect at the usually recommended doses. Maintenance of patients on a regular fixed dose of OCS may be used to replace the need for frequent bursts for recurrent exacerbations or for patients with chronic symptoms. This is common practice, although there is no firm evidence for its efficacy. Maintenance doses of OCS should be kept to a minimum in order to reduce the risk of side-effects. Whether the concomitant high dose of ICS should be reduced to low-to-moderate doses once maintenance of OCS therapy has been established is yet to be determined. Asthma control may not only be reflected in daily symptoms, use of reliever medication, emergency healthcare utilisation and OCS bursts, but may also be reflected in eosinophil counts in sputum, these have been used successfully to titrate ICS dose to minimise exacerbation rates in moderate asthma [16]. In severe asthma, both sputum eosinophils and exhaled nitrate may be useful in determining OCS dosage [17], but the possibility that measurements of sputum eosinophilia could help determine optimal OCS dose has not yet been studied.

Because of the lack of affordability of ICS in poorer countries OCS are commonly used at an earlier stage, sometimes even before the introduction of an ICS. On this basis, the definition of severe asthma in poorer countries may be different from that in richer countries, as recognised in the consensus by the World Health Organization (WHO) definition document of severe asthma [18].

Treatment of asthma with systemic corticosteroids therapy has been established since the introduction of cortisone, and prednisolone has become established as the most commonly used OCS with other preparations such as dexamethasone or betamethasone used less frequently. Systemic treatment with triamcinolone may be used for short periods treating those patients nonadherent to treatments [19, 20]. The use of prednisolone has been established through clinical experience. It is usually administered once daily in the mornings, and usually initiated at a dose of 40 $mg \cdot day^{-1}$ with a variable step-down regime over days or weeks to a minimum maintenance

dose level at which control of asthma is acceptable. In severe asthma cohorts approximately 33% are on OCS treatment at a median dose of 18 mg·day^{-1} [4–6, 8]. In addition, 54% of SARP patients needed more than three bursts of OCS in the past year [8].

Patients established on OCS should have their weight, blood pressure, glucose tolerance and bone density regularly checked. Prophylactic measures to prevent loss of bone density should also be taken. Weight gain caused by OCS is a particular issue as obesity may have a detrimental effect on asthma [21]. There is also the potential for increasing bacterial infections and for impairing macrophage function in severe asthma patients leading to decreased capacity to phagocytose bacterial particles [22, 23].

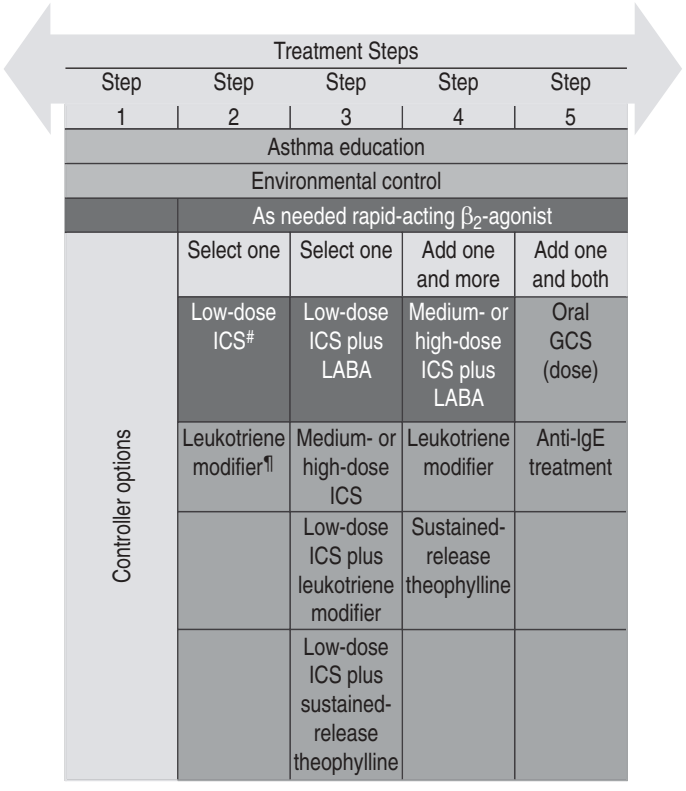

Figure 1. Stepwise approach to the treatment of asthma according to the Global Initiative for Asthma (GINA) guidelines. Patients with severe asthma are usually those requiring treatments at Step 4 or Step 5. ICS: inhaled corticosteroids; GCS: glucocorticosteroid; LABA: long-acting β-agonist; Ig: immunoglobulin. #: inhaled GCS; ¶: receptor antagonist or synthesis intubators.

β-adrenergic bronchodilators

β-adrenergic agonists provide beneficial bronchodilator and bronchoprotective (anticonstrictor) effects. The beneficial interaction of LABAs with ICS resulting in an improvement in the control of asthma is well documented [24–28]. However, the evidence has not yet been gathered for patients with severe asthma. A small study of OCS dependent asthmatics showed a poor bronchodilator response to β-agonists [29]. In SARP, 51% of severe asthma patients did not have a >12% improvement in their FEV1 after two puffs of albuterol, whilst 39% did not have >12% improvement with higher doses [8]. Many patients with severe asthma have significant chronic airflow obstruction that may or may not respond to β-adrenergic agonists [11, 12]. The mechanism for this profound reduction in response to the bronchodilator reaction to β-adrenergic agonists is unclear. Tachyphylaxis to the bronchoprotective effects, and less so to the bronchodilator effects, of short-acting β-agonists (SABA) and LABAs in asthma that is not reversed by the concomitant treatment with ICS has been demonstrated; however, the situation in severe asthma is unclear and has not been examined [30].

One of the potential issues with β-adrenergic therapy in patients with asthma is its excessive use, which may paradoxically lead to the deteriorating control of asthma or even death from asthma. This has been described in mild-moderate asthma patients who have been treated solely with SABAs without ICS with worsening of sputum eosinophilia and of the late asthmatic response [31–33]. The OR for nonfatal adverse events with formoterol was increased to 1.57 and for salmeterol to 1.14 when compared with the placebo in moderate asthma patients in whom some had been on concomitant treatment with ICS [34, 35]. By contrast other studies have not shown a significant increase in mortality or morbidity due to LABA use [36, 37]; however, a recent US Food and Drug Administation (FDA) meta-analysis concluded that patients on salmeterol (and not formoterol) not taking simultaneous ICS were at an increased risk of suffering an asthma-related event [38].

Patients with severe asthma are on high-dose LABAs in combination with on-demand SABAs *via* either a metered dose inhaler (MDI) or a nebuliser. In some asthmatics subcutaneous therapy with terbutaline may also be advocated, particularly those with severe sudden episodes of asthma deterioaration (type 1 brittle asthma) [39]. While no safe limit to the amount of β-agonists that can be allowed has been determined for severe asthma subjects, there have been case reports on the improvement in asthma control in severe asthma patients, who had previously taken very high doses, when there was a reduction in β-adrenergic treatment; this was despite the patients being on a high dose of corticosteroids [40].

The following issues regarding β-agonist therapy may be raised in severe asthma and the answer to these issues or indeed a consensus opinion will be very difficult to find or achieve. First, the general issue of limiting the number of inhalations of SABA used daily or the number of inhalations of ICS/LABA in combination used daily as a reliever and controller from one device need to be addressed, whether a limit can be imposed may be difficult to answer. Secondly, in patients with severe asthma and persistent symptoms who have been regularly using a LABA and need multiple doses of SABA per day for several weeks should: 1) the LABA be discontinued and the SABA be continued; 2) the SABA be discontinued and a short-acting anticholinergic agent be initiated; and/or 3) the LABA be discontinued and a long-acting anticholinergic agent be initiated?

Theophylline

Theophylline has been used as an additive controller in the treatment of severe asthma at Step 4 of the GINA guidelines. The beneficial effects of the addition of theophylline in severe asthma to already existent therapies are not known, but studies conducted in patients with moderate asthma at Step 3 of the guidelines show some benefit with better control of asthma [41, 42]. Intolerance with nausea, vomiting, headaches and gastrointestinal upset is common and often prevents therapeutic serum levels being achieved. Theophylline may improve corticosteroid sensitivity through HDAC2 recruitment [43, 44]. In an exploratory study of smoking asthmatics with corticosteroid insensitivity, theophylline with low-dose ICS improved peak expiratory flow rate (PEFR) and Asthma Control Questionnaire (ACQ) scores [45], but studies have not been performed in severe asthma patients regarding effect on corticosteroid sensitivity. Currently, it is an additive therapy that could be added at Step 4 in patients who can tolerate the treatment.

Leukotriene receptor antagonists

Leukoriene receptor antagonists (LTRA) have been shown to have beneficial additive properties when added to ICS therapy. Therefore, in patients where asthma is not sufficiently controlled with inhaled glucocorticoids alone, add-on therapies with montelukast to a constant dose of inhaled budesonide improves asthma control [46] to a level comparable with that achieved by doubling the dose of budesonide [47]. Add-on therapy with a cysteinyl leukotriene-1 (CysLT1) receptor antagonist enables a reduction in the dose of inhaled glucocorticoids required to control asthma [47, 48]. However, there have been limited studies in reported severe asthma. A small study did not find benefit to the addition of an LTRA in a nonslected group of severe asthmatics on LABA and ICS therapy [49]. Clearly, larger studies are needed, together with a study of the 5-lipoxygenase inhibitors, which may have the potential advantage of inhibiting neutrophilic inflammation.

Long-acting anticholinergic drugs

While long-acting anticholinergics are not part of the asthma guidelines at Step 4 or 5, they have been increasingly used in patients with severe asthma at these steps. A recent study indicates that when added to patients with asthma poorly controlled by an ICS alone, tiotropium, a long-acting anticholinergic, improved symptoms and lung function [50]. However, there is no data available yet on the addition of anticholinergics to patients already on LABAs. It is possible that one may encounter additional benefits on top of β-adrenergic agonists. Alternatively, long-acting

anticholinergics may be considered as an alternative for LABAs in patients without a bronchodilator response to LABAs or in cases of tachyphylaxis or excessive use of β-adrenergic therapies.

Anti-IgE therapy

The humanised monoclonal anti-IgE antibody omalizumab has been introduced as a treatment for severe allergic asthma. As an expensive therapy it is limited to the most severe patients with asthma. For example, the Institute for National Health and Clinical Excellence (NICE) in the UK advises its use only if a patient has had at least two asthma exacerbations within the past year that have needed admission to hospital, or when the person has had three or more severe exacerbations within the past year, one of which has needed admission to hospital, and the other two have needed treatment and monitoring in an accident and emergency department.

Omalizumab reduces free circulating IgE, leading to a reduction in high-affinity IgE receptors on basophils, and reduces eosinophilic inflammation. In severe allergic asthma, a significant reduction in exacerbation rates and improvement in aspects of quality of life, with little or no effect on lung function, has been reported [51]. A recent Cochrane review of all trials (including moderate and severe asthma) concluded that omalizumab was effective in reducing exacerbations as an adjunctive therapy to ICS and during steroid tapering phases of clinical trials [52]. However, in severe asthma it is unclear whether maintenance oral corticosteroids can be tapered to any significant extent. There were no specific characteristics that predicted a good therapeutic response. A good safety and tolerability profile has been observed [53]. Treatment is provided for an initial 4-month period, with an assessment made at the end to observe whether the treatment has been beneficial, and if positive it is then continued. There are no indications as to how long the treatment should be continued for. The cost-effectiveness of this therapy has been questioned [54].

Treatment with omalizumab is limited to a certain range of serum IgE levels depending upon body weight, many patients with severe allergic asthma cannot be prescribed the treatment because of either high levels of serum IgE or high body weight or both. A more potent anti-IgE antibody may be useful for this class of severe asthma patients and for treating those with much higher levels of serum IgE. The long-term effects of omalizumab on asthma are unknown, currently there is no advice on the duration of treatment needed. Another key issue is whether omalizumab would also be effective in nonatopic severe asthmatics who frequently have elevated serum IgE levels.

Corticosteroid-sparing agents

Several agents have been proposed as additive therapies that could lead to a reduction in the maintenance dose of OCS without a change in asthma control. These agents include low doses of methotrexate and cyclosporin A. Their mechanism of action as OCS sparing agents is unclear. Methotrexate may improve corticosteroid-binding characteristics of circulating peripheral blood mononuclear cells [55]. Double-blind, placebo-controlled studies of CS-dependent asthmatics have shown a beneficial effect of methotrexate and cyclosporine A in reducing the dose of OCS by approximately 40%, although placebo itself had steroid-sparing effects [56, 57]. The benefits of using these agents are small and may be associated with significant side-effects [58–60]. These agents should be restricted to a very small number where there are no other treatment options available. Chloroquine, gold salts and azathioprine have also been used as steroid sparing agents, but there is little published evidence that they are of benefit. There is insufficient evidence to use troleandomycin as an oral steroid sparing agent in asthma [61].

Disease heterogeneity and targeted therapies for specific phenotypes

Severe asthma is considered to be a heterogeneous disease. There is recognition of the heterogeneity of the inflammatory cell profile as measured by the analysis of sputum [62, 63] and

by the analysis of submucosal inflammation [64]. For example, based on sputum cell analysis, the inflammation can be eosinophilic, neutrophilic or paucigranulocytic. With molecular phenotyping the eosinophilic inflammation appears to be associated with high T-helper cell type 2 (Th2) cytokine expression, raised IgE levels and sub-basement membrane thickening [65]. Neutrophilic inflammation may be associated with more progressive airflow limitation [66]. Other aspects of inflammation including the role of mast cells, T-cells and macrophages have not yet been completely elucidated. In addition, the site of inflammation may be critical, predominantly affecting either small airways or large airways or both.

There is a large degree of remodelling change in the airways of severe asthmatics associated with subepithelial fibrosis and airway smooth muscle hypertrophy, and whether these changes are resultant or independent of inflammation is unclear. Indeed, a recent study compared bronchial biopsy findings between severe and nonsevere asthma, while there was a similar degree of inflammatory cell infiltrate in the two groups, there was a greater degree of subepithelial fibrosis and airway smooth muscle hypertrophy in the severe asthmatics compared with the nonsevere asthmatics [67].

Finally, a relative insensitivity to the effects of corticosteroids, and possibly to bronchodilators, is also present in severe asthma. The molecular mechanisms underlying these insensitivities have yet to be determined and could also be heterogeneous [68].

The potential new treatments available for severe asthma block very specific targets. One particular potential phenotype of asthma, which still needs further validation, is that of neutrophilic asthma characterised by an excess number of neutrophils in induced sputum that has been associated with a poorer response to corticosteroid therapy. Macrolides have been used to treat asthma associated with evidence of Mycoplasma or Chlamydia infection. However, a Cochrane analysis in 2005 concluded that there was insufficient evidence to support or to refute the use of macrolides in patients with chronic asthma [68]. More recently, in a study by STRUNK et al. [69] azithromycin was tried in a group of patients with moderate-to-severe asthma, more as an antineutrophilic agent than as an antibiotic. They showed azithromycin to be ineffective as an ICS-sparing agent in children with moderate-to-severe persistent asthma. However, in an 8-week treatment of severe refractory noneosinophilic asthmatics the reductions in neutrophilic indices of activation, such as interleukin (IL)-8 levels and sputum neutrophil numbers, were demonstrated together with improved quality of life scores but with no changes in lung function [70]. Other asthma phenotypes that are characterised on the basis of the pattern of asthma (*e.g.* recurrent exacerbations), or of chronic airflow obstruction (*e.g.* chronic irreversible airflow obstruction) have yet to be targeted with novel therapies.

The challenge of therapeutics for severe asthma is probably not entirely in the discovery of new targets, of which there are now many, but in the identification and validation of phenotypes of severe asthma. Therefore, in a syndrome as heterogeneous as severe asthma it could be predicted that well-defined subtypes may respond specifically to specifically targeted therapies. Monoclonal anti-IL5 antibody (mepolizumab) treatment has not been shown to have beneficial effects in moderate-to-severe asthma [71]; however, by targeting this specific treatment to patients with sputum eosinophilia, who have recurrent exacerbations, it will reduce the number of exacerbations without improving their lung function or other aspects concerning the control of asthma [72]. Thus, an anti-IL-5 approach would target specifically eosinophilic asthma, and indeed this specific therapy reduces exacerbation rates in such patients [72]. Figure 2 summarises the current approaches to the management and therapy of severe asthma and the interest in finding biomarkers that could lead to more specific and hopefully effective treatments for defined phenotypes.

Conclusions

Severe asthma remains a challenging condition both for the patient that continues to suffer from symptoms and side-effects of treatments and the clinician who struggles to manage individuals with a

condition for which there are many gaps in the evidence base. Given the complexity and heterogeneity of patients with severe asthma a dedicated systematic assessment is the logical way to ensure that the correct diagnosis is made, adherence is confirmed and comorbidities are addressed. This then provides the platform to allow logical trials of therapy. However, systematic assessment is only the beginning and we hope that over the next 10 years this will lead to more effective phenotyping of individual patients. Once this is achieved we will be able to improve the evidence base for treatment outcomes and long-term prognosis, as well as conduct logical clinical trials of the ever increasing number of new therapies under development for severe asthma.

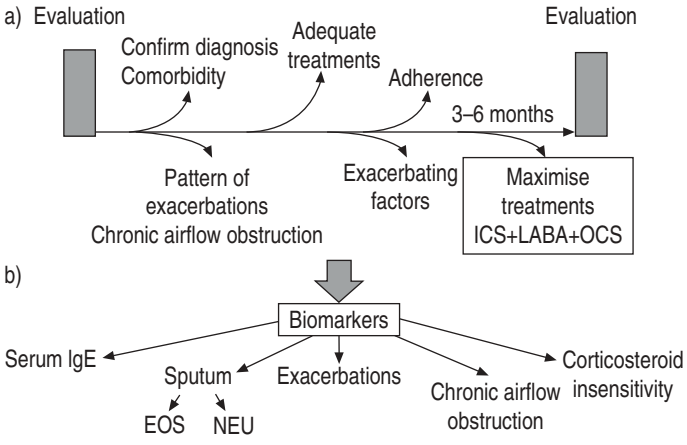

Figure 2. Management of severe asthma. a) The current approach to management of severe asthma with evaluation, observation and treatment maximisation with inhaled corticosteroids (ICS), long-acting β-agonist (LABA) aerosol plus the addition of an oral corticosteroid (OCS). Other controllers may also be added. b) The use of biomarkers that can provide some phenotyping of severe asthma on the basis of which new specific treatments could be tried. Ig: immunoglobulin; EOS: eosinophils; NEU: neutrophils.

Support statement

Q. Zhang was awarded an ERS Short-Term Research Fellowship in 2010 and has received research funds through Respiratory Biomedical Research Unit Grants, Royal Brompton and Harefield NHS Trust (London).

Statement of interest

K.F. Chung has been reimbursed for travel expenses to international meetings and received honoraria for speaking at meetings organised by GlaxoSmithKline, Novartis and AstraZeneca. K.F. Chung has participated in advisory boards of GlaxoSmithKline, Boehringer Ingelheim and Novartis, and received unrestricted research funding from GlaxoSmithKline and Pfizer, and has taken part in clinical trials organised by GlaxoSmithKline, Novartis and Asthmatyx. A. Menzies-Gow has received a medical education grant from Novartis. Travel to the ERS and ATS congresses has been funded by GlaxoSmithKline, AstraZeneca and Novartis. He has received lecture fees from GlaxoSmithKline, AstraZeneca and Novartis and participated in advisory boards for GlaxoSmithKline and Novartis. C. Hui has received research funds through grants from the Wellcome Trust and Asthma UK. He has received fees for lecturing from GlaxoSmithKline, AstraZeneca and Novartis. Travel to the ATS and ERS congress has been funded by GlaxoSmithKline and Asthma UK, and he has participated in an advisory capacity for GlaxoSmithKline. Q. Zhang received fees for lecturing from State Key Laboratory of Respiratory Diseases (The First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China) and travel to the Chinese National Cough symposium was funded by Wyeth.

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