Addressing the challenge of uncontrolled disease: identifying and effectively managing severe allergic asthma

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Introduction

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Approximately 5.6 million people in the UK have asthma.1 It is more prevalent in children than adults because it has a tendency to remit with age.2 Of those affected, an important minority (approximately 10%) remain symptomatic on a regular, typically daily basis despite maximal combination anti-asthma therapy i.e. inhaled and oral corticosteroids and other medicines, taken efficiently and regularly.3 Of these, at least 55% will be sensitised to one or more perennial, and sometimes also seasonal aeroallergens, such as house dust mite, mould spores, animal dander and pollens, and are therefore defined as having severe allergic or ‘atopic’ asthma.4

Epidemiological studies indicate that the prevalence of allergic rhinitis and eczema have increased in recent decades.5 In the past 20 years alone, the overall prevalence of these conditions in children has trebled in the UK.5 This trend has resulted in a similar, although less dramatic increase in asthma, since atopy is a predisposing factor. It is difficult to pinpoint one single specific cause of this allergy ‘epidemic’, but its rapid evolution and geographical variability (it has been observed primarily in ‘developed countries’) point to environmental influences.6 Changes in modern lifestyle and living conditions that have taken place over the past few decades in these countries have prompted the so called ‘hygiene’ or ‘microbial exposure’ hypothesis, which asserts that lack of exposure to microorganisms and their products resulting from cleaner homes has prevented a natural ‘switching off’ of our tendency to mount allergic responses early in life.7-9 In addition, the increase in double-glazed, centrally-heated households with high internal temperature and humidity may have contributed to creating conditions favoured by a common perennial allergen, the house dust mite.10

All disease is a burden and asthma is no exception. Asthma symptoms and exacerbations have been shown to impact significantly on quality of life, affecting sleep and the ability of sufferers to go to work or school, or to play, exercise and relax.11-13 Those with more severe disease live with the uncertainty of unplanned emergency visits to their GP surgery or local A&E Department11,12 and, for some, a fear of death.12 In the UK, approximately 1400 people die from asthma each year12 (more than three every day), reflecting both a failure of care and a failure to access medical help promptly enough during severe episodes. Consequently, a critically important element of effective asthma management is to empower sufferers to recognise how and when their disease deteriorates and to have a clear plan of what to do when this happens so that this fear may be set aside.

Despite their best efforts and maximal currently available treatment, patients with severe disease not only remain symptomatic, typically day and night, but are also much more likely to need ‘unplanned’ care involving visits to A&E and hospital inpatient stays2 and, not surprisingly, experience impairment of psychological well-being.14 Severe asthma also contributes disproportionately to the overall economic burden of the disease.15 The overall cost to the NHS of managing asthma (medicines, A&E visits, unscheduled GP visits and hospitalisations) is approximately £1 billion a year in the UK.16

About 80% of this cost was accrued in the management of 20% of people whose asthma is more severe.12 The cost to society is even greater, with 18 million working days lost due to asthma every year.12

Asthma management in the UK is guided by joint guidelines from Scottish Intercollegiate Guidelines Network (SIGN) and The British Thoracic Society (BTS).7 Most patients are typically known to their GPs and will have mild or moderate disease which can be well managed according to these guidelines. It is possible, however, that some patients may ‘slip through the net’, rarely visiting hospital except for the occasional setback, for example when they are affected by a chest infection or forget to renew their prescription. Patients with more severe disease, particularly if there is a problem with diagnosis or severe comorbidity (such as other chest diseases like bronchiectasis, which can sometimes accompany asthma or severe allergies) are more likely to be referred to a local hospital respiratory specialist team. Patients with unrelenting, severe symptoms who have been admitted to hospital on more than one occasion, or are frequent visitors to A&E, are also more likely to continue to be followed up by such a team or referred to a specialist tertiary referral centre. Such centres typically offer detailed and comprehensive analysis of asthma triggers, comorbidity and management, and specialist help for sufferers in terms of detailed action plans and hospital ‘passports’ detailing their optimal treatment in an emergency. They also offer a platform for inviting patients to participate in studies of the disease and in clinical trials of innovative therapies.

Objective, validated asthma diagnosis prior to treatment and assessment and management of co-existing allergic triggers can sometimes be extremely challenging, particularly in children. The joint SIGN and BTS Guidelines emphasise the importance of these issues and urge prompt referral of ‘difficult’ patients to specialist respiratory consultants.7 However, there is poor awareness of the diagnosis and management of allergic disease across the medical and allied health professions in both primary and secondary health care settings. This is partly because allergy is underrated and may be poorly taught in medical schools. This low awareness of the impact of allergy on diseases such as asthma is compounded by patients’ low expectations of symptom control. In common with other chronic diseases, people with asthma tolerate a poor quality of life rather than feel empowered to explore the cause and abolition of their symptoms.2 There is a pressing need to address this situation in order to improve patients’ quality of life and allergy fears at an individual level and, collectively, the associated societal and economic costs.
Severe allergic asthma

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Asthma is the most common long-term illness of childhood and affects 5.6 million people in the UK.1 The majority of asthmatics suffer from mild to moderate asthma that can be controlled by asthma medication up to step 3 of the British Thoracic Society (BTS) asthma guidelines.2 However, approximately 10% of patients have severe asthma that remains uncontrolled despite maximised treatment3 and a significant proportion of this group (approximately 40%) regularly take oral corticosteroids.4

In addition to the patient-specific impairment, management of severe asthma consumes a disproportionately high percentage of the whole asthma expenditure.5 Patients are at risk of severe asthma attacks and hospitalisation. In 2008−2009, there were over 79,000 emergency hospital admissions for asthma and at least two thirds of these admissions came through A&E.6 The severe asthma patient also suffers from treatment-related side effects, particularly when taking long-term systemic corticosteroids, in the form of hypertension, also suffers from treatment-related side effects, particularly when应急 hospital admissions for asthma and at least two thirds to step 3 of the British Thoracic Society (BTS) asthma guidelines.2 However, approximately 10% of patients have severe asthma that remains uncontrolled despite maximised treatment3 and a significant proportion of this group (approximately 40%) regularly take oral corticosteroids.4

The presence of other comorbidities such as gastro-oesophageal reflux disease (GORD), sleep apnoea and bronchiectasis, psychological morbidities including asthma panic, anxiety and depression, dysfunctional breathing patterns and upper airways dysfunction (vocal cord dysfunction), all lead to worsening symptoms and increased handicap.5 Faced with the complex and heavy burden of the disease, patients with severe asthma adopt different coping strategies, for example, poor adherence to medication.6

The severe asthma population is heterogeneous and a number of different phenotypes have been described. These include eosinophilic and paucigranulocytic asthma.7 In addition, around 78% of asthmatics aged 6−35, 72% of asthmatics aged 35−54 and 40% of asthmatics aged 55+ are atopic with a predisposition to generate high total serum immunoglobulin E (IgE).8 In this group, allergy seems to play an important role in disease initiation and severity.

Severe allergic asthma is defined as poor control despite optimal standard care and eliminating environmental allergens. The major increase in asthma and allergy incidence and prevalence over the last four decades is unlikely to be caused by changes in the genetic pool of the population, but through environmental changes which have been subject to much research.

The role of immunoglobulin E (IgE)

Immunoglobulin E (IgE) plays a central role in the pathogenesis of severe allergic asthma. It is produced by B-lymphocytes (B-cells) that switch classic immunoglobulin production from IgM to IgE under specific conditions that are optimally tuned to produce the allergic phenotype. Circulating total IgE is formed of specific (coding) and non-specific (non-coding) IgE, of which the latter constitutes the largest portion (>90%). Although we know that non-specific IgE production by B cells is not controlled by T-cells, the exact processes controlling its production and actual function are unclear. Specific (coded) IgE is produced by B-cells interacting through the major histocompatibility (MHC) receptor with T-helper cells type 2 (Th2) through the T-cell receptor (TCR).11 The TCR-MHC interaction is genetically constrained.

Inhaled antigens (e.g. house dust mite) are engulfed by antigen presenting cells (APCs), for example, dendritic cells in the lungs airspace mucosa, and are degraded into small peptides (epitopes) and presented with MHC on the surface of APCs ready to interact with a specific TCR. The T-cell’s development is genetically determined and tuned by Th2 cytokines such as interleukins 4, 5, 9 and 13 (IL4, IL5, IL9, IL13). The CD4+ T-cells with Th2 phenotype interaction with B-cells allows immunoglobulin class switching to IgE and production of specific (coded) IgE by B cells (plasma cells). The resulting free circulating specific IgE binds to high affinity IgE receptors (FcεRI) on mast cells and to low affinity IgE receptors (FceRII) on eosinophils. Upon second exposure to the specific antigen, the cross-linking of mast cell-bound IgE molecules by specific antigens leads to degranulation of mast cells and release of pro-inflammatory mediators such as leukotrienes, prostaglandins, histamine and tryptase.12

References

The allergic reaction


The early allergic reaction occurs within minutes of antigen (allergen) exposure and is characterised by symptoms in the upper airways such as itching and tearing in the eyes, sneezing, runny nose and throat itching, and in the lower airways as cough, wheeze, and cough, or in the skin, manifesting as flare and wheal with intense itching. The early allergic reaction is also associated with release of cytokines such as IL4, IL5, and IL13. IL5 is an eosinophil chemotactic and growth factor which is necessary for the recruitment of eosinophils to sites of inflammation, as well as their growth and maturation.

The late allergic reaction occurs 4 to 8 hours after allergen exposure and is characterised by mucus production, bronchial hyper-responsiveness and bronchoconstriction in the lower airways. Continuous allergen exposure leads to chronic allergic airway diseases in which the airway epithelium appears under the microscope to be broken (denuded), with intense inflammatory infiltrate of cells such as dendritic cells, lymphocytes, mast cells and eosinophils. Changes in structural cells such as epithelial and smooth muscle cells and fibroblasts are also present.

The broken epithelial barrier in the asthmatic airway facilitates allergen access to APCs and defence against other harmful substances such as air-pollutants, noxious gases and oxidants as well as infectious agents, either viral or bacterial, is impaired. Chronic inflammatory damage and mal-repair leads to excessive collagen deposition and airway scarring (remodelling) of the epithelial-mesenchymal trophic unit. The chronically inflamed asthmatic airway is ultimately narrowed and hyper-responsive to specific triggers such as allergens (e.g. dog hair, cat dander or moulds) and non-specific triggers such as strong smells, smoke and changing inhale air temperature. Consequently, severe allergic asthmatics experience ongoing asthma symptoms of breathlessness, tightness, cough and wheeze and are prone to severe attacks that can be life threatening.

In patients with allergic asthma, the total serum IgE level is raised with positive specific IgE to common aero-allergens such as house dust mite, pollens, cat dander, dog hair, and moulds (e.g. alternaria). Total serum IgE level fluctuates over time due to allergen exposure, for example, pollen sensitised individuals display higher levels during summer. Epidemiological studies have shown that total IgE levels correlate with prevalence of asthma and severity of asthma in younger patients.

The early and late allergic reactions in atopic subjects and eosinophilia are closely linked. However, there is a group of non-atopic asthmatics who display prominent blood or airway eosinophilia. Using gene signature analysis of blood and bronchial biopsies, one study reported the presence of Th2 high asthmatic phenotype marked by expression of cytokines such as IL5 and IL 13. Patients with a Th2 high phenotype (peroxin high group) responded better to ICS therapy and anti-IL13 monoclonal antibodies.

Excitingly for those working in the severe asthma field, several biologic therapies targeting various steps of the Th2 responses are being trialled which are likely to influence how we will treat severe asthma in the future.
Diagnosing severe allergic asthma

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Severe asthma represents a complex syndrome with many different clinical and inflammatory phenotypes. As such, there is no simple gold standard diagnostic test for severe and difficult-to-treat asthma and this has hampered the production of a clear definition. In the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) asthma guidelines, ‘difficult asthma’ is defined as persistent symptoms and/or frequent exacerbations despite treatment at step 4 or step 5.1 The most up to date definition is provided by an international consensus statement from the Innovative Medicines Initiative.2

The term ‘problematic’ asthma includes all asthma and asthma-like symptoms that remain uncontrolled despite the prescription of high intensity asthma treatment. It is an umbrella term that comprises patients with ‘difficult’ as well as patients with severe refractory asthma.

- **Difficult-to-treat asthma**: The term difficult-to-treat asthma is reserved for asthma where the poor control is due to comorbidities, poor adherence, or adverse psychosocial and environmental factors.

- **Severe refractory asthma**: The term severe refractory asthma is reserved for patients with asthma in whom alternative diagnoses have been excluded, comorbidities treated, trigger factors removed and adherence checked who still have poor asthma control or frequent severe exacerbations or can only maintain adequate control when taking systemic corticosteroids.

The distinction between severe refractory asthma and difficult asthma is important as the latter may not be candidates for high cost novel biologics. However, it remains a significant challenge to accurately identify, characterise and treat these patients.

A systematic approach to diagnosing severe, difficult-to-treat asthma

Difficult and severe asthma can be considered to be more like a syndrome, characterised by multiple phenotypes, and is very different from mild to moderate asthma. Consequently, people with difficult-to-treat asthma need a different approach, taking into account the heterogeneous nature of the condition. These patients require a rigorous and systematic approach to their diagnosis and treatment.3-6 Organisation of care should encompass a multidisciplinary approach and centres specialising in severe asthma are an effective way to deliver this.7

A severe asthma service provides the correct environment in which to optimise treatment, with a multidisciplinary systematic approach to the management of the disease, and aids in confirming the correct diagnosis and managing comorbid conditions. It is important for clinicians to undertake systematic assessment, identification and management of these conditions before considering increasing asthma pharmacotherapy.

The assessment should provide a staged and systematic approach to the difficult-to-treat asthmatic and there are a number of key questions to consider.

1. **Is it asthma?**
A number of conditions may mimic asthma and establishing a secure diagnosis is essential (see Table 1).

<table>
<thead>
<tr>
<th>Diseases that may mimic asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Pulmonary eosinophilic syndromes</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
</tr>
</tbody>
</table>

2. **Is it asthma plus...?**
Once a diagnosis of asthma is confirmed, it is important to identify other aggravating or coexisting factors that may complicate the disease. Particular attention should be paid to work place exposures, as occupational asthma is often under-recognised, accounting for between 9 and 15% of all cases of adult asthma.8 Multidisciplinary evaluation protocols have demonstrated that a significant proportion of patients with difficult-to-control asthma have identifiable factors contributing to poor control (see Table 2).3,4,9

<table>
<thead>
<tr>
<th>Factors contributing to poor asthma control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent exposure to triggers, allergens or irritants, or smoking</td>
</tr>
<tr>
<td>Psychosocial factors</td>
</tr>
<tr>
<td>Persistent poor adherence</td>
</tr>
<tr>
<td>Inhaler technique</td>
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<tr>
<td>Poor patient education/self-management skills</td>
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</tbody>
</table>

3. **Is it severe refractory asthma?**
Following systematic assessment, patients with difficult-to-treat asthma are either confirmed as having severe refractory asthma or given an alternative and/or additional diagnosis, including non-adherence. The next step is to attempt to further characterise these patients e.g. allergic or eosinophilic, in order to consider add-on, oral corticosteroid-sparing therapies such as omalizumab. Investigations used in the systematic assessment of severe, difficult-to-treat asthma are summarised in Table 3.5,7

† Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of omalizumab therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.
Allergic and non-allergic forms of asthma exist. Allergic asthma is the most common type and is associated with atopy. Atopy is defined as a genetic predisposition to produce immunoglobin E (IgE) against common environmental aeroallergens such as house dust mites, pollen, animal dander and moulds. Non-allergic asthma can be triggered by factors such as irritants, exercise, cold air, smoke, infection and anxiety.

In patients with allergic asthma, identifying the offending allergens (via careful history and diagnostic allergy tests) may be helpful so that exposure can be avoided or treated and exacerbations avoided. Two main categories of tests are available to assist clinicians in making an allergy diagnosis: skin prick tests and measurement of allergen specific IgE (s-IgE) antibodies from blood.

### Assessment of allergy

**Blood test**
- Eosinophil count
- Immunoglobulin (Ig) E
- Radioallergosorbent (RAST) test to aeroallergens including *Aspergillus fumigatus*
- Aspergillus IgG
- Anti-neutrophil cytoplasmic antibodies (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 provocative concentration causing a 20% fall in forced expiratory volume in 1 second (PC20)

**Imaging**
- Chest radiograph (CXR)
- High resolution computed tomography (HRCT) of the thorax
- Computed tomography (CT) of sinuses if indicated

**Multidisciplinary team (MDT) review as required**
- Ear, nose and throat (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

### Identifying high-risk patients

The use of asthma risk registers in primary care can reduce hospitalisation. Incorporating a proactive, structured approach to routine care with a focus on patient education, self-management skills, assessment of adherence, inhaler technique and asthma control is most effective. In particular, early review after an acute asthma exacerbation is important to reduce the risk of further attacks. A hospital based acute asthma follow up service has demonstrated evidence of poor compliance, poor inhaler technique, lack of written asthma management plans and undertreatment in a significant number of patients, which had not previously been recognised. In this study, a number of patients were also identified as more complex, requiring further evaluation in a specialist asthma clinic.

At an asthma review, ‘SIMPLES©’ provides a useful acronym for the main factors to check before considering escalating therapy or referral to secondary care.

### The SIMPLES© approach to the primary care management of ‘difficult to manage’ asthma

**Smoking status**

**Inhaler technique**

**Monitoring (Asthma Control Test [ACT], RCP ‘three questions’)**

**Pharmacotherapy (check non adherence), patient understanding**

**Lifestyle (environmental/occupational exposures)**

**Education**

**Support**

SIMPLES© Anna Murphy, 2012

### Conclusion

The management of severe, difficult-to-treat asthma requires a systematic approach that consists of correct diagnosis, identification of comorbidities and assessment of adherence. Many patients can be well controlled with existing therapies if simple measures are undertaken. However, some patients remain poorly controlled and will benefit from a systematic work up in a specialist asthma clinic.

### References

Severe asthma is a heterogeneous condition comprising several different phenotypes. Severe persistent allergic asthma is defined as poor control despite eliminating environmental allergens and optimal standard care. While dividing patients into clinical and inflammatory phenotypes has been helpful in improving our understanding of the disease, it has yet to fulfill the aspiration of targeted or personalised treatment for severe asthma, with the notable exception of anti-IgE therapy.

### Defining good control

Current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment, aligned with the pathway of the Global Initiative for Asthma (GINA).\(^1\)\(^ 2\) Good control, characterised by no symptoms, normal lung function and no exacerbations, is achieved by stepping up or down treatment as necessary.

The majority of patients with asthma have mild-to-moderate disease (steps 1 to 3) and the potential to be well-controlled with existing therapies (inhaled corticosteroids [ICS] and bronchodilators) if simple measures are addressed. Patients with severe asthma are at step 4 or 5 and require high dose ICS with or without oral corticosteroids (OCS) and the addition of other controller medications including long acting β\(_2\) agonists (LABA), leukotriene receptor antagonists (LTRA) and theophyllines. However, it is important that before escalating asthma treatment, simple measures including patient education, adherence, inhaler technique and asthma management plans have all been addressed. In particular, for allergic patients this should include removal of exposure to allergens wherever possible.

Often patients with severe asthma will require high dose ICS, frequent courses of OCS or continuous OCS in addition to other controller medications such as LABA, LRTA and theophylline. These patients have poor quality of life and the greatest morbidity and risk of mortality. In clinical practice, complete asthma control may currently be unachievable for many patients with severe asthma. Patients may have different goals and a wish to balance the aims of asthma treatment against the side effects of medication, particularly with oral corticosteroids.\(^3\) Therefore patients with severe asthma have an urgent need of innovative therapies to control their disease.

### Standard therapies

The adoption of asthma guidelines has meant that the management of mild-to-moderate asthma is now well established and ICS + LABA is an effective treatment for the majority of patients.\(^3\) Although very high doses of ICS are often used in patients with severe asthma, evidence suggests that ICS have a relatively flat dose-response relationship, and that the majority of benefit is achieved with lower doses (400–800mcg/day BDP or equivalent).\(^4\) Higher doses may increase the risk of systemic adverse effects for relatively little extra clinical benefit in many patients.\(^5\) However, there is individual variability in response to ICS and a trial of very high dose ICS may be warranted in some patients, particularly if the next step is consideration of continuous OCS. At this stage, it is important to consider the patient’s inflammatory phenotype before escalating steroid therapy.

### Add-on therapies

The benefits of treating moderate-to-severe asthma by adding LABA to ICS in terms of improving lung function, symptoms and reducing exacerbations have been demonstrated in many controlled studies.\(^1\) Other agents such as LTRA and theophylline may also be combined with ICS at step 3 or 4 although LABA remain the first choice as add-on therapy to ICS.\(^1\)

### Oral corticosteroids (OCS)

Current asthma guidelines offer few alternatives to OCS for the management of the subgroup of patients with severe asthma who remain poorly controlled despite high intensity treatment. For these patients optimal treatment should be aimed at achieving the best possible asthma control and quality of life with the lowest dose of medication (particularly OCS). Inhaled corticosteroids remain the most effective drug at reducing the requirement for long term systemic steroids.

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**Summary of stepwise management in adults**

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Patients with severe asthma often find their lives dominated by their disease. They live with the threat of a sudden asthma attack and cope with high day-to-day symptom levels whilst balancing the significant risk of comorbidities, in particular, side effects related to OCS. These include adrenal suppression, glucose intolerance, decreased bone mineral density, fractures, cataracts, glaucoma, anxiety and depression and impaired growth in children.6,7 Whilst the burden of asthma is well studied, the consequences of treatment particularly with long term OCS is often under-appreciated and rarely acknowledged in treatment comparisons when considering steroid-sparing agents.

Immunomodulatory agents

In the past, immunomodulatory drugs have featured in the search for effective steroid-sparing agents. However, cyclosporine, methotrexate, azathioprine and gold salts, have shown only marginal efficacy and their side effect profile can be significant leaving corticosteroids as the anti-inflammatory treatment of choice for severe asthma. Treatment with immunomodulatory agents should only be considered in a specialist centre with experience of using these medications to ensure appropriate patient selection.

Targeted treatments for severe asthma

It is clear that the majority of patients with mild-to-moderate asthma can achieve good control with standard therapies. However, for those patients still poorly controlled despite high intensity treatment, the lack of additional effective therapies is a significant challenge. Personalised treatment with targeted therapies remains a key goal in severe asthma management and, to date, the only approved targeted therapy for severe persistent allergic asthma is omalizumab (anti-IgE therapy).11 However, this remains an area of intense activity, with many monoclonal antibodies in development, and will hopefully bring the reality of personalised, targeted asthma treatment that bit closer.

Xolair® (omalizumab)

Dr Dinesh Saralaya, Consultant Respiratory Physician, Bradford Royal Infirmary, Bradford

Omalizumab (Xolair, Novartis Pharmaceuticals, UK) is a recombinant, humanised monoclonal antibody which targets immunoglobulin E (IgE) and inhibits the IgE-mediated inflammatory cascade generated by allergen exposure in asthma.

Omalizumab as add-on therapy has also been shown to improve asthma-related quality of life, symptom frequency and lung function.4,5,33 Most recently, 2-year data on the use of omalizumab show that improvements in asthma symptoms, reductions in healthcare utilisation and oral corticosteroid use are maintained on a long-term basis.7

Mode of action of omalizumab

Omalizumab is a humanised monoclonal antibody that selectively binds to IgE thus preventing the interaction between free IgE and its receptors on the mast cells and basophils. The resulting omalizumab-IgE complex prevents sensitisation of mast cells and basophils and minimises the potential for an anaphylactic reaction. In turn, this reduction in mast cell binding reduces mast cell degranulation and decreases the release of inflammatory mediators involved in severe allergic asthma (see Figure 1).

References


† Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab. Anaphylactic reactions were rare in clinical trials.
Omalizumab is administered subcutaneously either every two or four weeks at varying doses according to the weight of the patient and their baseline IgE level.

**Benefits of omalizumab as add-on therapy in severe persistent allergic asthma**

The efficacy and safety profile of omalizumab in severe persistent allergic asthma has been extensively investigated in randomised clinical trials and real-life asthma studies. The INNOVATE study was a 28-week randomised, placebo controlled, double blind study of the effect of omalizumab on clinically significant asthma exacerbations in 419 patients with inadequately controlled severe persistent allergic asthma. All patients were taking high doses of inhaled corticosteroids (ICS) (> 1000 mcg/day of beclomethasone dipropionate [BDP] or equivalent) and a long-acting beta-2 agonist (LABA). Approximately two thirds of patients were taking additional controller medication, including oral corticosteroids. Despite the high levels of medication use, 67% of the study population were considered to be at high risk of asthma-related death i.e. they had undergone previous intubation, visited A&E or been hospitalised in the previous year.

The INNOVATE study demonstrated that omalizumab as add-on therapy significantly reduced the rate of clinically significant exacerbations by 26% when compared to placebo (0.68 vs. 0.91; p=0.042) after post hoc adjustment for an observed imbalance in exacerbation history. Omalizumab also reduced severe asthma exacerbations by 50% (0.24 vs. 0.48; p=0.002) and the rate of total emergency visits by 44% compared to placebo (0.24 vs. 0.43; p=0.038). Significant improvement across all domains as assessed by the Asthma Quality of Life Questionnaire (AQLQ) (p≤0.002) was seen with omalizumab as add-on therapy.

Patients receiving omalizumab therapy represent, by definition, the population with severe disease, often requiring the regular, if not continuous, treatment with corticosteroids, which are not without side effects. The impact of omalizumab on OCS usage was evaluated in the Asthma Patient Experience on Xolair (APEX-1) study. In this 10-centre, retrospective review of medical records (NHS primary and secondary care) of 136 patients with severe persistent allergic asthma, for whom omalizumab was prescribed as part of usual clinical practice data, on OCS treatment (dosage and duration of treatment) and hospital visits for asthma in the 12 months before and 12 months after administration of omalizumab was extracted.

The mean reduction in total OCS prescribed per year was 34% (p<0.001) in the first 12 months after initiation of omalizumab as add-on therapy, compared to the 12 months before treatment (3.6g vs. 5.5g respectively). During the 12 months following omalizumab, 49% patients (n=66/136) stopped taking OCS.

Omalizumab was associated with a statistically significant 54% reduction in the number of asthma exacerbations per patient (3.67 events in the 12 months pre-omalizumab vs. 1.7 events in the 12 months post-omalizumab; p<0.001) and improved lung function. Treatment with omalizumab also led to a decrease in the use of healthcare resources, namely, reductions in A&E attendance (70% reduction; 0.46 A&E visits in the 12 months post-omalizumab vs. 1.52 A&E visits in the 12 months pre-omalizumab; p<0.001) and hospital admissions (61% reduction; 0.51 hospital admissions in the 12 months post-omalizumab vs. 1.30 hospital admissions in the 12 months pre-omalizumab, p<0.001) compared to the 12 months prior to initiation.

Further data on the real-life effectiveness of omalizumab in patients with severe allergic asthma has also been provided by a case report analysis in four UK centres (St Peter's Hospital, Chertsey, Bradford Royal Infirmary, Colchester Hospital and Derriford Hospital, Plymouth). Data over the 12 months (Plymouth) or 2 years (Chertsey, Bradford and Colchester) pre-omalizumab were compared with the most recent assessment after omalizumab initiation. Case report analysis showed statistically significant reductions (p≤0.001) in a number of parameters commonly used as measures of asthma severity: hospitalisation (80.6%; n=72, 252 events pre-omalizumab vs. 49 events post-omalizumab), hospital bed days (97.8%; n=50, 546 events pre-omalizumab vs. 46 events post-omalizumab), ICU admissions (Bradford Royal Infirmary only) (95.2%; n=49, 21 events pre-omalizumab vs. 1 event post-omalizumab), A&E visits (82.1%; n=74, 263 events pre-omalizumab vs. 47 events post-omalizumab) and GP visits (75.3%; n=51, 587 events pre-omalizumab vs. 145 events post-omalizumab). Patients were able to reduce their mean OCS usage by 62.8% (n=71; 15.6 mg/day pre-omalizumab initiation and 5.8 mg/day post-omalizumab initiation) and improve their asthma control level as assessed by the Asthma Control Test (ACT), as well as improve their quality of life as assessed by the AQLQ.

There is limited long-term data on the efficacy of omalizumab. A single centre, retrospective study of patients with severe asthma (n=45) who had been on omalizumab treatment for more than 23 months showed that long-term treatment reduces mean unscheduled hospitalisations or visits by 87% when compared to the pre-omalizumab period (30 events vs. 224 events, respectively). The number of patients taking oral corticosteroids reduced from 82% (n=37/43) to 42% (n=18/43) over the course of treatment and asthma symptoms, as measured by evaluation of lung function and asthma control scores, also improved. Among patients in employment or full-time education (n=17), there was a reduction in days lost due to asthma, equivalent to a mean 30 day increase per patient, per annum, in attendance at work or school.

† Clinically significant asthma exacerbation: worsening of asthma symptoms requiring treatment with systemic corticosteroids. Severe exacerbation: worsening of asthma symptoms requiring treatment with systemic corticosteroids and PEF or FEV1 <60% of personal best.

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**Figure 1: Slide reproduced with thanks to Dr Dinesh Sarvalaya**

- **Binds to free IgE**
- **Reducing high-affinity receptors**
- **Reduces allergic inflammation**
- **Prevents asthma exacerbations and reduces symptoms**
Overall, the real-life benefits of omalizumab have been studied in thousands of patients worldwide and the data consistently show that the benefits observed in clinical trials (namely, clinically relevant reductions in asthma-related events, reductions or optimisation of OCS usage, reductions in daily and night-time symptoms and improvements in quality of life) are effectively translated into real-life clinical practice.

Safety and tolerability of omalizumab

Pooled analysis of completed Phase I, II and III studies and international trials\(^2\)\(^3\)\(^1\)\(^1\)\(^2\)\(^1\)\(^3\)\(^1\)\(^4\)\(^1\)\(^5\)\(^1\)\(^6\) show omalizumab to be generally well-tolerated, with a frequency and severity of adverse events (AEs) similar to that observed with placebo. In the INNOVATE study,\(^2\) AEs were reported in 72.2% and 75.5% of patients in the treatment and placebo groups respectively. The most common AEs were nasopharyngitis (9.8% omalizumab, 9.3% placebo), lower respiratory tract infection (11.0% omalizumab, 10.1% placebo), headache (6.9% omalizumab, 9.3% placebo) and sinusitis (5.7% omalizumab, 7.6% placebo) and were generally mild-to-moderate in severity. The incidence of injection site reactions was higher in the omalizumab group (5.3%) than the placebo group (1.3%). Severe AEs were more frequent in the control group than in the omalizumab group (15.6 and 11.8% respectively).

Please refer to the Summary of Product Characteristics for further information regarding safety and special warnings and precautions.

Prescribing omalizumab

Guidance for the use of omalizumab was initially provided by NICE in 2007. It was reviewed and revised in April 2013\(^1\) and is now recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged six years and older who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year) and only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme. This updated guidance removes the requirement for patients to be hospitalised for asthma before being eligible for treatment as well as allow patients access to treatment from an earlier age. As a result, there is likely to be a broader patient population who may benefit from treatment with omalizumab.

References


Case study 1: Mrs JS (courtesy of Dr Dinesh Saralaya)

Mrs JS (aged 38 years) has been suffering with severe atopic asthma since she was 9 years old and her problems started to increase in 2006. Initially, she was maintained on a nasal fluticasone, a LABA, montelukast and oral aminophylline. Between 2009 and June 2011, when we started her on omalizumab therapy, she had recurrent courses of OCS but successfully avoided A&E attendance and hospitalisation by using a home nebuliser. In 2010, Mrs JS required continuous oral prednisolone (5 or 10 mg on alternate days), and she was swapped over to nebulised budesonide, inhaled formoterol and frequent salbutamol nebulisers plus the original oral aminophylline and oral montelukast and still successfully avoided hospitalisation. When omalizumab was initiated, Mrs JS’s baseline ACT and AQLQ were 9 and 3.1 respectively. By the time of her 16-week assessment, her ACT had risen to 23, her AQLQ to 6.8 and she had successfully ceased taking oral prednisolone. Since starting omalizumab treatment, she has not needed any courses of OCS or the use of nebulisers and she has also noted an improvement in her effort tolerance.

Case study 2: Mr PS (courtesy of Dr Dinesh Saralaya)

Mr PS is 41 years old, with a history of bronchial asthma since 1988, and presented with a life-threatening asthma exacerbation in June 2006. At the time of presentation he was taking high-dose inhaled corticosteroids, inhaled salmeterol, montelukast, lansoprazole and a salbutamol inhaler and had experienced three exacerbations requiring hospitalisation in the previous year.

Over the next three years, Mr PS averaged three hospitalisations a year and numerous unscheduled GP visits despite nebulised budesonide, inhaled formoterol, oral montelukast, oral aminophylline, carbocisteine and prednisolone 10 mg once daily. His IgE levels were elevated at 211 kU/L. When started on omalizumab in February 2009, Mr PS’s baseline ACT was 10 and his AQLQ was 4.3. By his 16-week assessment, his ACT and AQLQ had increased to 22 and 6.4 respectively. Since starting omalizumab treatment, Mr PS has had two hospitalisations and successfully removed oral prednisolone and carbocisteine from his treatment regimen.

At his last assessment, his ACT was still 22 and he showed consistent improvement in his AQLQ. He is now employed full-time and goes to the gym three times a week.
Asthma affects 5.6 million people in the UK,\(^1\) which means that one in nine people are affected by symptoms and exacerbations which impact significantly on quality of life, disrupting sleep and preventing the ability to go to work or school and, for some, to just play, exercise or relax.\(^2\)–\(^4\) The majority of patients with asthma have mild-to-moderate disease and, with a systematic approach to diagnosis and management, have the potential to be well-controlled with existing therapies (inhaled corticosteroids [ICS] and bronchodilators). However, approximately 10% remain severely symptomatic despite taking maximal combination anti-asthma therapy.\(^5\)

It is of continual, serious concern that these patients live with the threat of a sudden asthma attack, often requiring an emergency visit to their GP surgery or local A&E department, or hospitalisation or, for some, the fear of death,\(^3\) whilst balancing the risk of side effects related to long term use of corticosteroids.\(^6\)–\(^8\) There is a pressing need to address this situation, to improve patients’ quality of life and reduce the disproportionate economic burden that severe disease represents.\(^9\) In the first instance, we should be empowering all patients to recognise how and when their disease deteriorates, providing a proactive structured approach to routine care with a focus on education, self-management skills, assessment of adherence and inhaler technique. We need to work with our primary care colleagues to accurately identify, characterise and treat the group of patients who remain poorly controlled despite high intensity treatment and encourage referral either to respiratory specialists in secondary care or, if appropriate, directly to the specialist asthma service provided in the tertiary setting. Asthma risk registers can be employed to reduce hospitalisations.\(^10\)

Recognition that immunoglobulin E (IgE) plays a central role in the pathogenesis of severe persistent allergic asthma has allowed us to take a significant step forward in the pursuit of our goal of personalised treatment with targeted therapies.\(^10\)

We must now ensure that we use all the tools available in the most effective manner whilst continuing the pursuit of additional effective therapies.

References
UK abbreviated prescribing information

Xolair® (omalizumab) 75mg and 150mg solution for injection

Indications: Adults and adolescents (12 years of age and above): As add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long acting inhaled beta2-agonist. Children (6 to <12 years of age): As add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long acting inhaled beta2-agonist. Xolair treatment should only be considered for patients with convincing IgE-mediated asthma. Presentation: Pre-filled syringe of either 0.5ml omalizumab solution (75mg) or 1ml omalizumab solution (150 mg).

Dosage and administration: Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma. Children, adolescents and adults (6 years of age and older): 75–600 mg by subcutaneous injection every 2 or 4 weeks in 1–4 injections per administration. The appropriate dose and dosing frequency is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Patients whose baseline IgE levels or body weight are outside the limits of the dosing table in the Summary of Product Characteristics (SmPC) should not be given Xolair. Injections should be administered subcutaneously by a healthcare provider into the deltoid region of the arm, or alternatively, into the thigh. Treatment effectiveness should be assessed by a physician at 16 weeks before further injections are given. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Precautions: Not indicated for the treatment of acute asthma exacerbations, acute bronchospasm or status asthmaticus. Not studied in patients with autoimmune diseases, immune complex-mediated conditions, pre-existing renal or hepatic impairment, hyperimmunoglobulin E syndrome, allergic bronchopulmonary aspergillosis or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of Xolair therapy is not recommended. Immune system disorders: Type I or local or systemic allergic reactions, including anaphylaxis may occur. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair, but some started beyond 2 hours and even beyond 24 hours after the injection. Medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following the administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. Anaphylactic reactions were rare in clinical trials. Antibodies to Xolair have been detected in patients treated with humanized monoclonal antibodies including omalizumab. Onset typically 1–5 days after first or subsequent injections, also after long duration of treatment. Symptoms include arthritis/arthritis, rash, fever, lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder. Patients should be advised to report suspected symptoms. Patients with severe asthma may rarely present with systemic hypersesinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome).

In rare cases, patients on anti-asthma therapy may present or develop systemic eosinophilia and vasculitis. In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, parasanal sinus abnormalities, cardiac complications, and/or neuropathy. Parasitic (helminth) infections IgE may be involved in the immunological response to some helminth infections. The helminth infection rate in the overall clinical programme was less than 1 in 1000 patients. Caution may be warranted in patients at high risk of helminth infection. Drug interactions: Based on the clearance of Xolair there is little potential for drug–drug interactions. No formal drug interaction studies have been performed. There is no pharmacological reason to expect that commonly prescribed medications used in the treatment of asthma will interact with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated. Undesirable effects: Very Common (≥ 1/10): pyrexia (children 6 to <12 years of age), Common (≥ 1/100 to <1/10): abdominal pain upper (in children 6 to <12 years of age), headache (very common in children 6 to <12 years of age) and injection site reactions such as pain, erythema, pruritus, swelling. Uncommon (≥ 1/1000 to <1/100): dizziness, nausea, diarrhoea, dyspeptic signs and symptoms, urticaria, rash, pruritus, photosensitivity, weight increase, fatigue, swelling arms, influenza-type illness, somnolence, paraesthesia, syncope, postural hypotension, flushing, pharyngitis, coughing, allergic bronchospasm. Rare (≥ 1/10000 to ≤1/1000): anaphylactic reaction, other serious allergic conditions, anti-omalizumab antibody development, parasitic infection, laryngoeoeda, angioedema. Not known: Idiopathic thrombocytopenia (including severe cases), Churg-Strauss syndrome, alopecia, arthralgia, myalgia, joint swelling, serum sickness, fever, lymphadenopathy. Arterial thromboembolic events (ATE) In controlled clinical trials and an observational study, a numerical imbalance of ATE was observed. In a multivariate analysis controlling for baseline cardiovascular risk factors, the hazard ratio was 1.32 (confidence interval 0.91–1.91). In an analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24–5.71). Platelets No pattern of persistent decrease in platelet counts, as observed in non-human primates has been reported in humans. Isolated cases of idiopathic thrombocytopenia (including serious cases) have been reported in the post-marketing setting. Parasitic infections: Numerical increase in rate not statistically significant; course, severity and response to treatment unaltered. Prescribers should consult the SmPC for full information regarding other side-effects. Quantities and basic NHS price (excl. VAT): 75mg pre-filled syringe, £128.07 and 150 mg pre-filled syringe, £256.15. Marketing authorisation numbers: EU/1/05/319/005, EU/1/05/319/006 and EU/1/05/319/007 (75mg) and EU/1/05/319/008, EU/1/05/319/009 and EU/1/05/319/010 (150mg). Legal category: POM. Date of last revision of prescribing information: December 2013. Full prescribing information is available from: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Telephone: (01276) 692255, Fax: (01276) 692508.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis (01276) 698370.

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