Ther Adv Chronic Dis
2017, Vol. 8(2-3) 31–45
DOI: 10.1177/2040622317690494

Targeting patients with asthma for omalizumab therapy: choosing the right patient to get the best value for money

Abir Al Said, Breda Cushen and Richard W Costello

***Abstract*:** The asthma syndrome has many manifestations, termed phenotypes, that arise by specific cellular and molecular mechanisms, termed endotypes. Understanding an individual's asthma phenotype helps clinicians make rational therapeutic decisions while the understanding of endotypes has led to the development of specific precision medications. Allergic asthma is an example of an asthma phenotype and omalizumab, a monoclonal antibody that neutralizes serum immunoglobulin (Ig)E, is a specific targeted treatment which was developed as a result of an understanding of the endotype of allergic asthma. Omalizumab has been widely used in clinical practice in Europe for over a decade as an add-on therapy to treat patients who have severe refractory allergic asthma. Over this period, many centres have reported their experience with omalizumab as an add-on therapy in patients with severe asthma. These 'real world' clinical effectiveness studies have confirmed the benefits, cost-effectiveness and clinical utility of this medication. Combining the outcomes of both sources of research has yielded important insights that may benefit patients with severe asthma, clinicians who treat them, as well as the funding agencies that reimburse the cost of this medication. The purpose of this review is to describe how to identify and evaluate a patient with asthma for whom treatment with omalizumab may be of clinical and cost-effective benefit. The assessment and investigations used to confirm allergic asthma, the objective assessment of adherence to asthma therapy and the expected benefits of add-on omalizumab treatment are described.

Keywords: Severe asthma, allergic asthma, exacerbations, adherence to therapy

Received: 23 August 2016; revised manuscript accepted: 22 December 2016.

Correspondence to:
Richard W Costello
Department of Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin 9, Ireland.
rcostello@rcsi.ie

Introduction

For the majority of patients with asthma, inhaled corticosteroids (ICSs) and long-acting beta-agonists (LABAs) control symptoms, improve lung function and reduce exacerbations. However, about 10% of all asthma patients require additional therapy to achieve asthma control. Choosing which therapy to give these patients has been aided by our understanding that asthma has many clinical manifestations, termed phenotypes which arise by specific mechanistic pathways, known as endotypes. Allergic asthma is an example of an asthma phenotype and omalizumab, a monoclonal antibody that neutralizes serum immunoglobulin (Ig)E, is a specific targeted treatment which was developed as a result of an understanding of the underlying mechanism of allergic asthma.

Omalizumab has been widely used in clinical practice in Europe, the United States (US) and other regions, for over a decade as an add-on therapy to treat patients who have severe refractory allergic asthma. Over this time randomized trials and 'real world' clinical effectiveness studies from many centres have identified the clinical utility of this medication. Despite these data, clinicians still face challenges in managing these patients, for example identifying whether a patient is sufficiently adherent to other therapy to warrant adding omalizumab, whether to use this or

new alternative monoclonal antibodies and for how long to continue treatment. For funding agencies that reimburse the cost of this medication, challenges remain in identifying its true cost-effectiveness.

The purpose of this review is to describe how to identify and evaluate a patient with asthma for whom treatment with omalizumab may be of clinical value. The assessment and investigations used to both confirm allergic asthma and demonstrate that it is truly refractory as well as the controversies in calculating a true picture of the cost-effectiveness of add-on omalizumab treatment are described.

Endotype and phenotypes in asthma

By a variety of processes, asthma results from changes in the calibre of the airways. Investigators have used ways to define subgroups of asthma that share particular features, termed phenotypes, or common pathophysiological cellular, molecular and other mechanisms, termed endotypes.[1–3] Allergic asthma is a common and prototypic example of an asthma phenotype. In allergic asthma exposure to an allergen, to which an individual is sensitized, leads to typical asthma like responses, often in association with upper airway symptoms, atopic eczema, as well as systemic allergic responses.

The molecular mechanisms of the allergic asthma phenotype

The underlying pathways that lead to the allergic asthma phenotype are relatively well established. Central to the response is an exogenous peptide to which an individual is sensitized. The mechanism through which sensitization occurs is a complex interaction of genetic and environmental exposures that occurs principally in infancy and early childhood. Following exposure to the allergen, epithelial cells release alarmins including interleukin (IL)-33, IL-25 and Thymic stromal lymphopoietin (TSLP) while dendritic cells ingest and present the antigen to T-cells.[4] Activation of these T-cells in this environment leads to production of the Th2 cytokine repertoire, IL-4, IL-5, IL-9, and IL-13. Of these cytokines, IL-4 promotes B-cell differentiation to produce IgE. Binding of IgE to FcεRI receptors on mast cells promotes differentiation, maturation and prolongation of survival of mast cells in the airways. FcεRI/II receptors are also expressed by epidermal Langerhans cells, eosinophils, mast cells, basophils on antigen-presenting cells, and hence IgE has a pleiotropic effect of controlling the production of important immune mediators (cytokines, interleukins, leukotrienes, and prostaglandins) that promote inflammation.[5]

The clinical features of the allergic asthma phenotype

Typical clinical features of allergic asthma are the tendency for the condition to manifest early, often in childhood and with a male predominance. Exercise-induced bronchospasm is reported to occur more frequently and be more severe in patients with allergic asthma compared with those with other phenotypes of asthma.[6,7] The severity of symptoms may vary through the year, in a manner that corresponds to the seasonal variations in the particular allergen to which the individual is sensitized. Allergic asthma is associated with other systemic features including conjunctivitis, atopic dermatitis and rhinitis as well as in some cases nasal polyps and chronic sinusitis.[8] The presentation of these associated conditions is often discordant over time with asthma, for example rhinitis may be more clinically active than asthma at certain times in life.[9] Seeking these features in a clinical interaction will help a clinician identify a patients as having an allergic phenotype of asthma.

Several observational cohort studies have used cluster analysis to identify features of asthma.[10–18] The various clusters of patients with atopy have often been quite heterogeneous in terms of symptom severity, pulmonary function, and tendency for exacerbations. In some studies, the symptoms have been rated as relatively mild, with few exacerbations, easy control with ICSs and preservation of lung function. By contrast, some have reported patients with high levels of symptoms and poor asthma control even with high strength ICSs. Besides the bias of differing selection criteria and sources of recruitment, these data suggest that there is no uniform course for allergic asthma. This is not too surprising given that among individuals there are wide variations in both the level of exposure to allergens and the adherence to preventer medication.

To start selecting the correct patient for omalizumab the diagnosis of asthma must be correct

Typically, the evaluation of a patient with asthma starts with the clinical history. As straightforward

as this may sound, the history must be carefully evaluated to seek features that are consistent with the diagnosis of asthma. Extensive literature reporting the experiences of clinics dedicated to the treatment of patients with severe asthma indicates how incomplete and inaccurate the diagnosis of asthma may be. For example, in a study of 304 patients with physician diagnosed asthma, McGrath and Fahy reported that 23% did not have evidence of bronchial hyperresponsiveness.[19] Others have reported that conditions such as stridor from upper airway disease, unrecognized cystic fibrosis, chronic obstructive pulmonary disease (COPD) overlap syndrome, anxiety and obesity are all common asthma mimics.[20] Features to be sought in the patient history include a sizeable variation in the symptoms of cough, wheezing and shortness of breath which result from variation in airflow through the conducting airways. One such characteristic feature is that the symptoms occur at night, awakening the patient with either cough or shortness of breath.[21,22] Other characteristic features include onset of prolonged symptoms following exposure to environmental exposures, in particular allergens, as this is the central feature of allergic asthma.

Patient-reported symptoms vary greatly between individuals. Many patients do not perceive their symptoms in a manner that reflects disease severity as would be identified in other tests, such as assessment of airway inflammation or lung function, while others attribute dyspnoea to asthma as opposed to co-existing conditions such as deconditioning.[23,24] Given that the history can be an unreliable way to make the diagnosis of asthma, the first task is to ensure that the diagnosis is accurate and assessed using objective measures. The tests required for a correct diagnosis of asthma are outlined below.

There is no one diagnostic test which can be used to make a certain diagnosis of asthma unlike, for example, pathological analysis of tissue to make a diagnosis of cancer. Instead, asthma is considered to be present in an individual when similar airway conditions are excluded and characteristic features are evident.[25,26] The defining characteristic of asthma, first used in the precise definition of asthma over 50 years ago, 'is a widely varying obstruction of the conducting airways that occurs over a relatively short period of time'.[27] The cause of the variation in airflow may be due to the irritating effect of endogenous mediators, such as inflammatory cell products induced by environmental or other stimuli, accompanied by exaggerated neural reflexes or structural changes which may lead to hyperresponsiveness of the airways.[28] This definition requires that specific features in the history, such as nocturnal or exercise associated wheezing is present or nocturnal dyspnoea is reported, in addition, tests that are sensitive to changes in airway calibre should be performed repeatedly over a period of time to establish the diagnosis of asthma. The diagnosis is further supported by evidence of other characteristic features including airway inflammation and airway hyperresponsiveness.

Objective measures of changes in the calibre of the conducting airways

Since the diagnosis of asthma is dependent on detecting significant changes in the calibre of the conducting airways over short periods of time, it is important that all efforts are made to achieve this measurement. The measurements need to be reproducible, they must reflect clinically meaningful changes in the conducting airways and the test needs to be performed often enough to detect these changes. The most commonly used method, spirometry, is highly reproducible but not very sensitive to changes in the small airways.[29] Reversibility testing, a significant change in airway calibre in response to an inhaled beta agonist, is often used as the gold standard for the diagnosis of asthma. There are well recognized limitations of this surrogate measure, for example reversibility testing is not possible when patients have normal spirometry. On the other hand, reversibility testing may not show significant changes in airflow when patients have severe obstruction due to airway inflammation. In an example such as this, a period of treatment with anti-inflammatory therapy may be required before changes in airflow are achieved. In both of these cases, the reversibility test will fail to make the diagnosis of asthma. Hence, spirometry needs to be performed repeatedly, both at times when the individual is well and when they are symptomatic. Barriers such as ease of access to the test, which, for quality control, is usually performed in specialist laboratories, can be a significant limiting factor in achieving sufficient tests to achieve a diagnosis.[30]

Impulse oscillometry is a simple, non-invasive method that uses the forced oscillation technique, requires minimal patient cooperation and is suitable for use in both children and adults.[31] This method can be used to assess obstruction in the large and small peripheral airways and has been used to measure bronchodilator response and bronchial provocation testing. Data have shown that impulse oscillometry is a useful test to diagnose, monitor the clinical course, assess bronchodilator responses and predict loss of asthma control in both adults[32–38] and the paediatric population.[32] The sensitivity of the test and ease of use make this an attractive alternative to spirometry testing for some patients. However, the same limitations of access so that repeated measures can be obtained, as described for spirometry, apply for this test.

Another method of detecting changes in the calibre of the airway that overcomes the limitations of tests performed in laboratories outlined above, is through the use of electronic peak flow meters. Previously, patients recorded the results of peak flow recordings to paper diaries. Unfortunately, it was shown that these paper diaries were unreliable as patients did not persist in recording the data, or the recordings were not accurate. Electronic peak flow recordings are a valuable resource and they are increasingly being used to make an accurate diagnosis of asthma, in particular when patients understand the need for monitoring as a way of both making a diagnosis of asthma and understanding asthma precipitants.[39]

Bronchial challenge in the diagnostic evaluation of patients with severe allergic asthma

Demonstration of increased reactivity of the airways to irritant stimuli provides supporting evidence of the diagnosis of asthma. Typically, the stimuli used are exogenous bronchoconstrictor agents such as methacholine or endogenous agents such as histamine or mannitol, meaning that both direct and neural reflex responses are involved.[40,41] Individuals with allergic asthma typically react to these inhaled agents, with a reduction in airway calibre at doses several log orders below responses seen by people who have healthy lungs and do not have asthma. In people with a likely clinical diagnosis of asthma, for example among symptomatic people exposed to occupational irritants, the test bronchial provocation has positive and negative predictive values of 41.1% and 95.2%.[42] This means that a negative test effectively excludes asthma. The positive prediction test is lower because other airway conditions, including cystic fibrosis and COPD, demonstrate a reduction in airway tone in response to these agents.[43,44] The absence of bronchial hyperresponsiveness in a symptomatic individual essentially excludes asthma.[45]

Airway inflammation in allergic asthma

Characteristically, the airways of patients with allergic asthma are inflamed with Th2-lymphocytes, eosinophils and mast cells. These cells localize to smooth muscle and airway nerves as well as goblet and epithelial cells.[46] Allergens, viruses and other stimuli that initiate exacerbations and promote asthma symptoms induce prototypic immune responses that result in the recruitment, activation and release of inflammatory mediators from these cells. Products such as eosinophil granule proteins, prostanoids, leukotrienes and histamine influence the function of these resident cells to lead to mucous production, cough and airway narrowing.[47,48] Inflammation of the airways can be assessed by sampling the airways directly, for example by endobronchial wall biopsy, indirectly with induced sputum, or by assessing the immune response through blood sampling. Bronchial biopsy is a valuable way to directly assess airway inflammation, detect the products of inflammatory cells and to understand structure function interactions. However, relative to the surface area the small samples, cost and inconvenience to the patient limit this test to specialist centres or research. Induced sputum has the advantage of being a non-invasive test to detect eosinophils[49] but few centres use the test instead peripheral blood eosinophil levels are used as a surrogate. Both sputum and peripheral blood eosinophils, again by association, reflect the immune response, in particular eosinophil trafficking as these cells migrate from the bone marrow to the airways. The stability of peripheral blood eosinophilia should be demonstrated by repeated measures, as concurrent use of oral corticosteroids lowers blood eosinophil levels. Notwithstanding the limitations of each these tests, the presence of tissue, sputum or elevated blood eosinophils help in refining the diagnosis of the asthma phenotype.

Fractional exhaled nitric oxide (FeNO) has been established as a non-invasive surrogate marker of airway inflammation. The 2011 American

Thoracic Society (ATS) clinical practice guideline recommends that FeNO > 50 ppb in symptomatic patients can be used to identify allergic type airway inflammation that may respond to corticosteroids.[50] This recommendation is based on the finding that patients with severe uncontrolled allergic asthma who have increased FeNO have been shown to have persistent eosinophilic airway inflammation despite therapy with inhaled and systemic steroids.[51,52]

Demonstrating allergy

The presence of IgE against specific allergens is the hallmark of the allergic phenotype, hence this test is essential in the diagnostic pathway outlined below. Allergen-specific testing by skin prick puncture tests or by demonstration of allergen-specific IgE by *in vitro* fluorescence enzyme-labeled assays such as by ImmunoCAP must be demonstrated, although the latter is more specific. In practice, even by extensive laboratory testing in some people with an elevated peripheral blood IgE, no specific allergen can be identified. It is noteworthy that there is little evidence that either the absolute levels nor changes in the levels over time are of practical clinical significance. This may be because the local regulation of IgE levels are more relevant to the determination of the allergic phenotype.[53,54]

Severe and difficult to manage asthma

As outlined above, allergic asthma is just a phenotype, which means that both symptoms and the frequency of exacerbations can vary among individuals. While many patients can be controlled with symptomatic reliever therapy and regular preventer ICSs, some remain uncontrolled with high levels of impairment and at risk of exacerbations. Clinicians face a significant challenge to correctly manage patients with severe allergic asthma. Guidelines for the management of asthma indicate that when disease stability or symptom control is not achieved while on ICS treatment it may be due to several causes, such as poor adherence, poor inhaler technique or continued exposure to environmental factors/triggers, or other comorbid conditions.[55–58] The relationship between levels of inhaler adherence and asthma control that support these recommendations are well described. For example, Ismalia and colleagues conducted an observational retrospective cohort study looking at the relationship with inhaler adherence and asthma exacerbations in 19,126 Canadian asthmatic patients treated with salmeterol/fluticasone.[59] Adherent patients had lower rates of systemic corticosteroid use, emergency room visits, general practitioner visits, hospitalizations and respiratory specialist reviews. Patients that were persistent with this level of adherence also had a lower rate of asthma related exacerbations (0.19 *versus* 0.23, $p < 0.001$). Overall the authors showed a 24% increased risk in having an exacerbation when nonadherent with salmeterol/fluticasone treatment. Surprisingly, research has also shown that adherence is a particular problem among patients attending severe asthma clinics. For example, in 2009, Gamble and colleagues reported on the prevalence of nonadherence in patients attending a specialist 'difficult' asthma clinic. Of the 182 patients reviewed, 35% of the patients had collected 50% or fewer prescriptions for ICSs, 45% collected somewhere between 50–100% of prescriptions and only 21% had collected 100% of their prescriptions for ICSs.[60] In another study conducted in a specialist severe asthma centre in Leicester, UK, 65.2% of asthmatic patients on ICSs had <80% prescriptions dispensed.[61] Hence, there is good evidence even among patients with severe asthma to support guideline recommendations to assess adherence and inhaler technique in patients with allergic asthma before changing medications.

Identification of poor inhaler adherence and inhaler technique

Somewhat of an 'elephant in the room' though is how poor adherence and poor inhaler technique can be identified. The Global Initiative for Asthma (GINA) document recommends asking a patient in 'an open manner' about their adherence to medication. Unfortunately, studies have shown that self-report is itself biased by poor self-recall or misinformation given by the patient to please a healthcare provider.[62–64] Currently, there are approximately 58 different tools for capturing self-reported adherence. In a recently published systematic review of self-reported adherence scales, only 16 of these 58 had any published data on reliability.[65] Hence, for making a clinical decision as important as advancing therapy to an agent such as a monoclonal antibody or even continuous oral corticosteroids it is essential that objective measures of adherence and inhaler technique be obtained. Pharmacy dispensing data are an efficient way of determining an estimate of the persistence of medication use, in other words

generally speaking how much of the time the patient had the medication and whether they continued to use the prescription. However, prescription dispensing data do not indicate how often the individual used their medication. Some more novel methods of assessing adherence include electronic audio recording devices which when attached to an inhaler identify both when and how well the inhaler was used.[66] Another method to measure adherence in a select asthma population is FeNO suppression. In a study published by McNicholl and colleagues, patients with a high FeNO level were followed for 5 consecutive days receiving directly observed inhaled steroid therapy.[67] Patients who were deemed nonadherent, based on previous pharmacy refill records, had a significantly greater reduction in their FeNO level than those who were adherent, suggesting that FeNO may be used to differentiate patients with difficult asthma who are adherent and those who are not. This practical test may be especially useful in patients with allergic asthma who are being considered for add-on omalizumab therapy, as such patients have an elevated FeNO.[68]

Having identified poor inhaler adherence or poor inhaler technique or persisting allergic exposure, it is possible to improve asthma control in patients with allergic asthma using education interventions supplemented with reminders or feedback to promote medication adherence.[69,70] Environmental assessment can help detect ongoing exposure to an allergen and should be considered through home visiting or home monitoring to identify and reduce continuous allergen exposure.[71] The key message of this aspect of assessment of a patient with allergic asthma is to use objective measures to help guide clinical decision making through this critical evaluation stage.

Omalizumab

For those patients who remain uncontrolled despite treatment with high dose ICSs and LABAs, and who are also adherent to this therapy and demonstrate good inhaler technique, add-on therapy may be required. For patients with allergic asthma, omalizumab, a humanized anti-IgE monoclonal antibody that inhibits the serum IgE is licensed as an additional therapy in the USA, Europe and other parts of the world. Omalizumab binds to the constant region of circulating IgE molecule and prevents free IgE from interacting with the high and low-affinity IgE receptors (FcεRI and FcεRII). By reducing the levels of circulating IgE the medication is effective regardless of allergen specificity.

When administered at therapeutic doses, omalizumab rapidly reduces free serum IgE levels by over 95% and also results in the reduction of receptor density on the mast cells or basophils, in turn leading to a decreased allergen-stimulated mediator release response. Dependent on the patient's weight (40–120 kg) and IgE levels (30–1500 IU) omalizumab at a dose between 150–375 mg is administered subcutaneously every 2 or 4 weeks, with a maximum dose of 750 mg every 4 weeks. A recent report from an Australian registry showed similar clinical benefits in those patients with IgE levels above the dose range at the highest dose in patients.[72]

Indications for the use of omalizumab in asthma

In 2003, the US Food and Drug Administration approved the use of omalizumab in the USA, as a subcutaneous injection, for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs. In 2005, the European Medicines Agency (EMA) approved the use of omalizumab as an add-on therapy for the treatment of inadequately-controlled severe persistent allergic asthma, despite the use of high dose ICSs and LABAs in patients aged 6 years or over. Specifically, omalizumab may be used if patients have a positive skin test result for an allergy caused by an aeroallergen, reduced lung function (less than 80% of normal) as well as frequent asthma symptoms and must have had at least two severe 'exacerbations' of asthma. It is noteworthy that the indications for the use of this therapy varies between regions as do thresholds for funding. For example, in the UK, omalizumab is approved only for patients over 6 years old who have severe allergic asthma and at least four courses of oral steroids in the prior year.[73] Typically, a 16-week trial period is performed before a global physician assessment of the medication's efficacy is performed, after which a decision on future use of the therapy is made.

Clinically important side effects

The most common adverse reaction from omalizumab is injection site induration, injection site itching, injection site pain, and bruising.

Table 1. The results of events on omalizumab and placebo as individual severe exacerbation rates from the 12 randomized clinical trials of omalizumab as add-on therapy for patients with severe asthma.

Author	Events on omalizumab	No events omalizumab	Events on placebo	No events on placebo	RR	95% CI
Bardelas[91]	21	115	34	111	0.63	0.26–1.5
Busse[92]	39	268	60	257	0.62	0.43–0.9
Busse[93]	15	190	25	180	0.18	0.28–0.08
Hanania[94]	152	275	179	242	0.75	0.6–0.9
Holtgate[95]	13	126	15	120	0.83	0.4–1.6
Humbert[96]	35	246	55	236	0.61	0.4–0.9
Lanier[97]	56	384	59	192	0.47	0.34–0.65
Li[98]	22	288	33	266	0.61	
Milgrom[99]	56	384	59	109	0.68	0.43–1.07
Ohata[100]	6	151	18	164	0.36	0.15–0.9
Soler[100]	35	274	83	272	0.42	0.3–0.6
Vignola[101]	43	209	59	196	0.68	0.49–0.96

CI, confidence interval; RR, relative risk.

As may be expected in patients with a clinically important tendency to allergy and a history of respiratory illness, both allergy and anaphylaxis, but no fatal events, have been reported to occur after administration of omalizumab. In registration clinical trials such events were estimated to occur in 0.1% of patients and in postmarketing reports were estimated to occur in at least 0.2% of patients, based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. As a result, licencing agencies mandate that omalizumab must always be administered in a healthcare setting, by healthcare staff appropriately equipped with and trained to administer therapy in response to such events.

In a pooled analysis of randomized studies, malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in omalizumab-treated patients were a variety of types, with breast, nonmelanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. Registry studies have shown that there are no conflicting safety concerns with regard to oncological incidence nor pregnancy. These data suggest that while there is always a safety concern with any relatively new medication there is neither clinical evidence nor a plausible mechanism to suggest a concern for omalizumab.[73]

Clinical value of omalizumab as add-on therapy for patients with uncontrolled asthma

The international European Respiratory Society (ERS)/ATS guidelines on definition, evaluation and treatment of severe asthma, suggested a therapeutic trial of omalizumab was needed both in adults and in children with severe asthma. This document placed higher value on the clinical benefits from omalizumab in patients with severe allergic asthma and lower value on increased resource use.[29] The reason for this recommendation extends from both results of several randomized clinical trials as well as from observational studies performed on patients in clinical settings. The results of these have been described in detail elsewhere but are updated and summarized below (and in Table 1).

The results of late-phase clinical trials with study periods up to 12 months have shown that omalizumab reduces both the frequency of asthma exacerbations, steroid medication burden, quality of life measures and lung function. A summary analysis of 12 clinical trials of 6427 patients showed that the therapy, when used as an add-on medication to ICSs and LABAs was associated

with a lower risk of exacerbations at the end of the study, relative risk (RR) 0.57, and a reduction in corticosteroid therapy [RR 1.80, 95% confidence interval (CI) = 1.42–2.28], see Table 1.[74] Similar but less impressive trends in improvement in other measures of asthma have also been reported. For example, the Asthma Quality of Life Questionnaire (AQLQ), score was 0.33 higher in omalizumab-treated patients compared with control patients (95% CI = 0.27–0.38) but this is not above the minimal clinically important difference of 0.5. Similarly, rescue medication was lower in those treated with omalizumab, reduced by 0.5 puffs/day (95% CI = −0.28 to −0.25) and peak expiratory flow significantly increased by 15 l/sec in the omalizumab-treated group and 3 l/sec in the control group (95% CI = 8.1–15.5). While most trials were conducted in patients with evidence of a sensitization to a specific allergen, recent small randomized trials of patients with elevated IgE, but no identifiable specific allergic response, showed similar benefits.[75] Hence, the results of randomized clinical trials in patients with allergic asthma have identified that omalizumab reduces exacerbations of asthma but does not have reproducible effects on asthma quality of life scores nor on measures of lung function. These data indicate that when trying to identify which patients with allergic asthma may benefit, a physician needs to concentrate on asthma attacks as the feature most likely to be improved by the therapy.

Results of real world studies

The results of real world studies indicate that patients with allergic asthma treated with omalizumab have a high burden of clinical illness, including moderate or severe airflow obstruction, significant use of oral corticosteroids, rhinitis and obesity. This suggests that clinicians select patients who also have severe allergic asthma but also have high healthcare costs and comorbidity from corticosteroids and by inference they wish to see these conditions also influenced by the therapy.[76] The results of registry observational studies and pragmatic trials show that within 16 weeks of starting treatment, similar benefits as those reported in the randomized trials are seen. Severe exacerbations decline by between 75–82%[77] by 6 months, with overall reductions in exacerbations between 41–84%.[77] Interestingly, reductions in severe exacerbations are sustained over the next 2 years by 70%.[78] Asthma-triggered hospitalizations in the year after starting therapy are reduced by between 50–96%[79] and similarly emergency department attendance, a particular feature of severe asthma, decrease by up to 53% in the first year[80] and decrease by 80%[81] in the first 3 years of omalizumab therapy. Additionally, as might be expected, the studies showed a significant decline in the proportion of patients experiencing daytime symptoms on a daily basis by between 69% at 16 weeks[82], 53% at 6 months,[78] and up to 58% and 83% reduction at 1 and 2 years, respectively.[83] Similarly, night-time symptoms decreased by up to 72% over the first 16 weeks[83] which was sustained at between 51–84% over the first 6 months of treatment, extending to 72–90% over 2 years.[78] In most studies lung function also improved; in the first 16 weeks of treatment, forced expiratory volume in 1 s (FEV1) improved by 8–22% and improvement rates over 1 year ranged from 7–25%.[83] These data not only support the more rigorously performed controlled clinical trials but suggest that the benefit of the medication extends to effect clinical practice.[79] One study which simply counted the direct costs of therapy with the overall cost savings identified that, per omalizumab responder, patient treatment costs for 6 months were 834 euro lower in those treated with omalizumab.[84]

The role of patient selection and adherence to inhaled therapy in evaluating the clinical effectiveness of omalizumab

As outlined in detail above, selecting the correct patient for therapy with an agent such as omalizumab is a clinical challenge. Centres that lack the necessary breath of specialist testing and clinical experience may not recognize patients with allergies and asthma that have their symptoms driven by other conditions. Furthermore, a notable limitation of all the randomized clinical trials and registry studies of omalizumab as an add-on therapy was that, contrary to the published guidelines, before adding omalizumab, no study objectively assessed prior adherence (Costello, unpublished systematic review). Because clinicians lack an objective measure of adherence and therefore struggle to objectively identify which patients are truly refractory to current therapy, meaning that some patients may be prescribed the medication, when cheaper alternatives such as correctly used inhaled therapy are available. This also means that it is possible that nonadherent patients enrolled in clinical trials benefited from the use of an active

medication, thereby enhancing the apparent benefit of omalizumab. Studies performed with electronic monitoring devices currently underway (e.g. ClinicalTrials.gov identifier: NCT02307669) could identify the interaction of poor adherence to therapy and outcomes in patients with severe asthma treated with omalizumab.

Contrasting results from randomized clinical trials and clinical outcomes studies

Unlike is the case with most clinical effectiveness studies, real world evidence with omalizumab in patients with severe asthma not only replicates the benefits of randomized clinical trials but suggests additional benefits. One explanation for the different outcomes is that these effectiveness studies do not usually report the long-term follow-up results of those patients who do not continue with the medication, because usually if the person does not improve in 16 weeks the treatment is discontinued. This means that the real world studies are enriched by responders. Another consideration is the general benefit in clinical practice of a scheduled review with an asthma specialist nurse, who administers the treatment, cannot be ignored. Through access to regular care the benefit of reduced rates of treatment of exacerbations through emergency departments and unscheduled care appointments may have been reduced. Nonetheless, the consistency of the data with the additional value that the studies extend over years rather than the shorter time frame of the early randomized trials indicates the clinical benefit of add-on omalizumab in patients with severe allergic asthma.

Cost-effectiveness of omalizumab

The data outlined above suggest that there are clear clinical benefits to add-on therapy with omalizumab for poorly controlled patients with allergic asthma. The cost of therapy is a concern and healthcare systems have not always funded omalizumab, for example there are considerable differences between the EMA approval and UK National Institute for Health and Care Excellence (NICE) recommendations for use.[85,86] From a clinical point of view, exacerbations are meaningful and costly, and studies suggest improved lung and quality of life when the duration of therapy is extended to assess the impact for some years. However, while the clinical data are relevant, omalizumab as an add-on therapy for asthma, has largely not been shown to be cost effective (see Table 2).[87] The lack of cost-effectiveness is due in part to the current methods of estimating the cost-effectiveness of add-on therapy. The difficulties in establishing a case to fund add-on therapy for patients with severe and uncontrolled allergic asthma are outlined below.

Table 2. Results of cost-effectiveness of omalizumab from the seven studies of trials of omalizumab as add-on therapy for patients with severe asthma. Data are adapted from Lai and colleagues[91,108,109]. see enclosed:https://s100.copyright.com/AppDispatchServlet?author=Tianwen%20Lai%2C%20Shaobin%20Wang%2C%20Zhiwei%20Xu%2C%20Chao%20Zhang%2C%20Yun%20Zhao%20et%20al.&cc=by&contentID=10.1038-%2Fsrep08191&issueNum&publication=Scientific%20Reports&publicationDate=2015-02-03&publisherName=NPG&title=Long-term%20efficacy%20and%20safety%20of%20omalizumab%20in%20patients%20with%20persistent%20uncontrolled%20allergic%20asthma%3A%20a%20systematic%20review%20and%20meta-analysis&volumeNum=5

Source	Country	ICER
Brown[102]	Canada	€821,000/QALY
Campbell[103]	USA	$287,200/QALY
Dewilde[104]	Sweden	€56,091/QALY
Dal Negro[105]	Italy	€26,000/QALY
Nooten[106]	Netherlands	€38,371/QALY
Oba[107]	USA	€378 /0.5-point AQLQ increase
Wu[108]	USA	$821,000/QALY

AQLQ, Asthma Quality of Life Questionnaire; ICER, Incremental cost-effectiveness ratio; QALY, quality adjusted life year

Conventional cost-effectiveness models

A cost-effectiveness model typically attempts to quantify the tangible benefits of a medication including its effects on quality of life and compare these with the cost of the therapy.[88] Using conventional models, the cost-effectiveness of omalizumab therapy is constrained by the fact that omalizumab is a monoclonal antibody, which involves an expensive manufacturing process. While most long-term observational studies support beneficial outcomes beyond reducing asthma exacerbations, exacerbations are not expensive given that treatment consists of relatively inexpensive oral corticosteroids.

Clinical outcomes not assessed in the current cost-effectiveness models

This current cost-effectiveness model does not take into account some practical issues. Omalizumab was first developed for use in allergic rhinitis and several early randomized trials have focused on its value in controlling this condition. These preliminary phase II studies showed clinical benefit in particular improvements in measures of quality of life. However, while the impact of rhinitis and sinusitis for patients are reported to be very high the health economic arguments are not so substantive, as these conditions are not associated with expensive healthcare costs, such as emergency department visits or hospital admission. This means that in practice a tangible clinical benefit that is achieved is not easily translated into the health economic model that is confined purely to asthma related features.

Oral corticosteroids are the mainstay of management of exacerbations and for some patients they are also used as maintenance therapy. However, as is well documented these medications have enormous long-term clinical side effects including type 2 diabetes, cataracts, osteoporosis, cardiovascular and psychological events. These secondary conditions carry very significant economic and clinical costs that need to be counterbalanced with the direct low cost of corticosteroid therapy.[89]

Clinicians recognize the immense clinical and long-term value of avoiding the use of oral corticosteroids, even if they are low cost.[90] Clinicians and patients also recognize the additional value of omalizumab in reducing other allergic related coexisting pathologies such as rhinitis and sinusitis. Hence, economic models should be more comprehensive, by including rhinitis quality of life scores, corticosteroid-related impacts on quality of life and costs associated with the side effects of this therapy.

When to stop therapy; another aspect of cost-effectiveness

There is no direct evidence to indicate that omalizumab has an obvious disease-modifying effect, hence there is no definite answer to the question of how long or how short the duration of therapy should last. In Europe, registry and other studies indicate that many patients once started remain on omalizumab, but a median duration of therapy appears to be about 5 years. A recent randomized trial (XPORT, ClinicalTrials.gov identifier: NCT01125748) may help in making this decision. In this study patients treated effectively with omalizumab were randomized to stay on therapy for a 6th year ($n = 88$) and others were randomized to placebo for a year ($n = 88$). Over the 6th year of treatment there was a 19.35% (95% CI 5–30%, $p < 0.01$) absolute difference in prevention of exacerbations in the group who continued on omalizumab. Similarly, asthma control was superior and time to first exacerbation was delayed in the group who continued therapy with omalizumab. It is noteworthy that in pharmacokinetic studies it took 1 year for the IgE levels to return to pretreatment levels. These studies are suggestive that rather than having a disease modifying effect, omalizumab continues to work against continued allergen-induced IgE production. Hence, the duration of therapy should be based on factors such as impact of the treatment and ongoing allergen exposure, as well as the cost-effectiveness for that individual.

The widening field of additional therapy for patients with severe asthma

Several new therapeutic options are now licensed for the treatment of patients. Most recently, monoclonal antibodies directed against IL-5, which, by depleting bone marrow eosinophil deployment, reduce asthma exacerbations, in particular viral exacerbations. The steps to choose anti-IL-5 therapy are similar to those for omalizumab, and are largely based on the levels of peripheral blood eosinophilia, which, as listed, is also a feature of allergic asthma. These agents also have a benefit for patients with severe asthma with frequent exacerbations, which are most likely viral in nature. While there are no likely drug–drug interactions, cost will prevent use of both medications simultaneously. In time, clinical studies will provide objective data as to which patients benefit from which agent but in its absence a clinical decision based on the clinician's judgement of the most dominant precipitant, viral infection or allergy will be required.

Summary and recommendations

A pattern of clinical features accompanied by objective evidence of variations in lung function and the presence of immunological tests to specific allergens identify a distinct phenotype of asthma. The severity of the allergic asthma ranges from a mild intermittent form to a sustained

severe form that requires a considerable medication burden to control. Add-on therapy with omalizumab is an option for the management of difficult-to-control patients with allergic asthma, as randomized clinical trials convincingly show significant improvements in objective and subjective parameters of exacerbations. Furthermore, real world clinical effectiveness studies, which enrich for patients who respond to an initial trial of therapy, also support trial results and due to longer duration of follow up show that these medications also yield greater symptom control and improvement in measures of lung function. However, both physicians and healthcare systems face many challenges in providing this therapy to the correct patients.

Firstly, physicians need to correctly confirm the diagnosis, they must rigorously ensure good adherence to currently prescribed therapy in particular ensuring correct inhaler technique and advise the patient on methods to minimize exposure to allergens. Technologies that allow for this are now becoming more widely available to make this task more straightforward. Healthcare agencies need to develop an understanding that conventional models of cost-effectiveness do not incorporate clinically relevant events such as the avoidance of high risk, low cost medications such as oral corticosteroids. Overcoming these two challenges can ensure that this add-on medication can be provided to the appropriate patient with severe uncontrolled allergic asthma.

Acknowledgements

The authors are grateful to Shane Sullivan Novartis, Dublin, Ireland and Dr Ismail Kasujee, Respiratory Franchise Novartis, Basel, Switzerland for assistance in identifying data and discussions on cost-effectiveness.

Funding

RWC is supported by a HRB Clinician Scientist award CSA/19 and HRB DI/59.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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