

Omalizumab therapy in the management of severe allergic asthma

Alessandra Concas
Fulvia Chieco-Bianchi
Maria Rita Marchi
Luciana Paladini
Andrea Vianello

Respiratory Pathophysiology and Intensive Care Division, University - City Hospital of Padova, Padova, Italy

Address for correspondence:

Andrea Vianello, MD
Respiratory Pathophysiology and Intensive Care Division
University - City Hospital of Padova
Padova, Italy
E-mail: avianello@qubisoft.it

Summary

Severe asthma is defined as a condition which can result in risk of frequent severe exacerbations (or death), adverse reactions to medication, and/or chronic morbidity, despite maximal therapy. Although patients with severe asthma represent only 5-10% of the asthmatic population, they represent the major burden of illness and impairment of Quality of Life (QoL), constituting a real clinical challenge for pulmonary physicians. Omalizumab, a humanised monoclonal antibody which binds free immunoglobulin E (IgE) in the serum, has demonstrated to be effective as add-on therapy to improve asthma control in adults and children with severe persistent allergic asthma that is uncontrolled by standard drug treatment. Our review discusses the efficacy and safety of omalizumab and offers practical recommendations for its use in patients with severe asthma.

KEY WORDS: severe asthma; Immunoglobulin E; omalizumab; lung function.

Introduction

Asthma is a heterogeneous disease characterized by different patterns of airway inflammations resulting in a cascade response, including infiltration of the mucosa, mucus hypersecretion, sub-basement membrane fibrosis, smooth muscle hypertrophy, epithelial loss and alterations of angiogenesis. The result of this complex interaction is airway obstruction, a final effect of airway inflammation and remodeling changes (1).

Asthma constitutes a global health problem affecting over 300 million individuals of all ages, ethnic groups and countries. Annually, approximately 250,000 people are estimated to die prematurely due to asthma (2). While most patients reach full clinical control on conventional inhaled corticosteroids and beta2-agonists, a relevant proportion of the asthmatic population develops exacerbations and cannot achieve clinical stability

While most patients reach full clinical control on conventional inhaled corticosteroids and beta2-agonists, a relevant proportion of the asthmatic population develops exacerbations and cannot achieve clinical stability despite maximal therapy.

despite maximal therapy, and therefore suffer "severe asthma" (3). Although patients affected by severe asthma represent only 5-10% of the asthmatic population, they are responsible for the major burden of illness and impairment of Quality of Life (QoL), representing a challenge in clinical management and a huge impact on healthcare resources. In fact, despite advances in knowledge of the past few decades, severe asthma still consumes up to 50% of the total health cost of asthma, due to hospital admissions, use of emergency services and unscheduled physician visits (4-6).

Omalizumab, a humanised monoclonal antibody which binds free Immunoglobulin E (IgE) in the serum, was approved in 2003 by the US Food and Drug Administration (FDA) and in 2005 by the European Medicines Agency as add-on therapy to improve asthma control in adults and children with severe persistent allergic asthma. A number of controlled clinical trials has subsequently demonstrated its efficacy and safety in the treatment of severe allergic asthma uncontrolled by standard drug treatment. On the basis of such considerations, our review discusses the efficacy and safety of omalizumab and offers practical recommendations for its use in patients with severe asthma.

Characteristics of severe asthma

Definition

There are many definitions of severe asthma and this variability accounts for difficulties to evaluate the burden and scope of the disease. The most recent and widely known definition has been developed by the WHO: according to the level of current clinical control and risk, severe asthma is defined as "uncontrolled asthma

Severe asthma is not a single disease, but rather a many-sided condition that can be subdivided into different phenotypes.

which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medication and/or chronic morbidity (including impaired lung function or reduced lung growth in children)” (7).

In the literature, severe asthma has also been defined as difficult-to-treat asthma, therapy-resistant asthma, steroid-dependent asthma, and brittle asthma (8). In particular, the term “difficult asthma” was used for the first time in 1999 by an European Respiratory Society (ERS) Task Force (9), while the American Thoracic Society (ATS) used the term “refractory asthma” in the following year (10). ATS and ERS definitions also account for treatment involved in the management of the disease, since patients are labelled as having severe asthma when they need oral steroids or high-dose inhaled steroids to remain under control and continue to suffer from asthma symptoms despite proper maintenance therapy (Table 1). Thus, each of these definitions implies the assessment of disease control, exacerbating factors or comorbidities, and therapeutic response during an observational period of at least 6 months (11). It is important to emphasize that severe asthma is not a single disease, but rather a many-sided condition that can be subdivided into different phenotypes, on the basis of several features. Definition of phenotype is based on symptoms, health status, asthma control, airway obstruction (variable or partially fixed), bronchial hyperresponsiveness, atopy, inflammation, exacerbations and response to treatment. As a consequence, several, different clinical phenotypes can be defined: frequent exacerbators including near-fatal episodes, individuals with irreversible airway obstruction,

and patients with oral corticosteroid dependency or resistance (8). Additional phenotypes are characterized on the basis of date of symptom onset, triggers, such as aspirin sensitivity, or prevalent characteristics of airway inflammation, that is eosinophilic, neutrophilic and pauci-granulocytic (12-14). Finally, it should be noted that asthma control may be influenced by other variables, such as environmental exposures, comorbidities, adherence to therapy, and inhalation technique. In particular, comorbidities play an important role in determining the poor control of asthma symptoms, including rhinosinusitis or previous surgery for nasal polyps; use of aspirin or NSAIDs, beta-blockers, angiotensin converting enzyme inhibitors, or estrogens; gastroesophageal reflux disease; obstructive sleep apnea; menstruation influence; psychiatric disease history; and obesity (15).

Classification

Despite the development of practice guidelines including systems for classifying the severity of the disease, there is no agreement about classification of asthma by severity, due to the fact that severity is not a stable feature of asthma but may change with time (16); in addition, the term “severity” may have different meanings, including the description of current symptoms, the resistance to standard treatment or future risk of death and exacerbations (7,15,17). As a consequence, a standardized classification of severe asthma is still required, in order to properly identify and treat patients and to reduce the burden of the disease. Table 2 summarizes the main components of asthma severity.

Table 1 - ATS Workshop consensus for definition of severe/refractory asthma. Definition requires 1 or both major criteria and 2 minor criteria. It also requires that other conditions have been excluded, exacerbating factors have been treated, and patient is generally compliant (Adapted from 10).

Major characteristics

1. Treatment with continuous or near continuous (50% of year) OCSs
2. Requirement for treatment with high-dose ICSs

Minor characteristics

1. Requirement for additional daily treatment with a controller medication (e.g., long-acting beta2-agonist, theophylline, or leukotriene antagonist)
2. Asthma symptoms requiring short-acting β -agonist use on a daily or near-daily basis
3. Persistent airway obstruction ($FEV_1 < 80\%$ predicted, diurnal peak expiratory flow variability $> 20\%$)
4. One or more urgent care visits for asthma per year
5. Three or more oral steroid bursts per year
6. Prompt deterioration with $> 25\%$ reduction in oral or ICS dose
7. Near-fatal asthma event in the past

Table 2 - Components of asthma severity (Adapted from 7).

- A. Level of control
 - current clinical control (impairment): symptoms and functional limitation over previous 2-4-wk
 - exacerbations over previous 6-12 mo, including number, severity and use of systemic corticosteroids
- B. Level of current treatment prescribed, inhalation technique and compliance with treatment
- C. Responsiveness to treatment
- D. Risk

There are several potential reasons for suboptimal outcomes of patients with severe asthma, which can be summarized as follows:

1. Untreated severe asthma: patients with persistent symptoms who are inadequately treated, but whose condition improves when proper treatment has been established.
2. Difficult-to-treat severe asthma: the poor response to treatment reflects the presence of factors other than asthma that may contribute to poor symptom control, i.e., comorbidities which may represent an important trigger to asthma symptoms (18).
3. Treatment-resistant severe asthma, including:
 - a. asthma for which control is not achieved despite the highest level of recommended treatment (refractory asthma and corticosteroid-resistant asthma)
 - b. asthma for which control can be maintained only with the highest level of recommended treatment (7).

Pathology

The ability to identify different phenotypes (possibly by non-invasive methods) is a critical aspect of the treatment of severe asthma, since this should be based on a personalized approach.

Two important cellular patterns of severe asthma have been reported: a) predominant eosinophilic inflammation, seemingly unresponsive to treatment with high-dose corticosteroids, and/or b) predominant neutrophilic inflammation (19). Individuation of different inflammatory phenotypes in severe asthma has meaningful implications for patient treatment, due to the heterogeneous response to

steroids, ranging from absolute lack of response to therapy to reduced responsiveness. The ability to identify different phenotypes (possibly by non-invasive methods) is a critical aspect of the treatment of severe asthma, since this should be based on a personalized approach.

Another important component of the pathobiology of asthma is represented by airway remodelling. Remodelling is characterised by thickening of the lamina reticularis and structural changes of the epithelium (epithelial shedding, subepithelial fibrosis, inflammatory cells infiltration), submucosa (myofibroblast proliferation, goblet cell hyperplasia), smooth muscle (hyperplasia and hypertrophy) and vasculature (neovascularization) of the airway wall. The combination of airway remodelling and hyperresponsiveness is typical in severe asthma and can lead to chronic airway obstruction (20,21).

Therapeutic options

By definition, severe asthma is a condition characterised by patients' symptoms for which control is not achieved by maximum treatment with inhaled therapy; for this reason, effective treatment is a major unmet need in severe asthma. Usually, control of symptoms can be achieved by using combination inhalers that contain both corticosteroid and long-acting beta2-agonist as reliever therapy, in addition to maintenance

Several broad-spectrum anti-inflammatory therapies that target neutrophilic inflammation are still in development, but they have shown adverse effects following oral administration.

treatment, including inhaled corticosteroids, long acting beta2-agonists, leukotrien antagonists, sustained-release theophyllines and eventually oral corticosteroids (22). However, despite maximum dosage, patients may not reach stable clinical conditions. Clinical trials evaluating bronchodilators with an extremely long duration of ac-

tion, such as vasoactive intestinal peptide analogs, potassium-channel openers and the combination of long-acting anticholinergic bronchodilator with beta2-agonist are in development (23,24). New blockers of specific mediators, including prostaglandin D(2), IL-5, IL-9, and IL-13, are being studied and could be potentially effective on specific subtypes of severe asthma (25). Several broad-spectrum anti-inflammatory therapies that target neutrophilic inflammation are still in development, but they have shown adverse effects following oral administration. Macrolides might benefit some patients with infection by atypical bacteria, in particular patients with predominant neutrophilic asthma. Steroid resistance is a leading problem and drugs that may reverse this resistance, such as theophylline and nortriptyline, have been proposed. In selected patients with severe asthma, bronchial thermoplasty can represent an effective approach, although clear evidence of efficacy is still lacking (26-29). Current and experimental therapeutic options for severe asthma are listed in Table 3.

Omalizumab therapy

Omalizumab (Xolair®, Novartis), a recombinant humanized monoclonal anti-IgE antibody, has been approved as add-on treatment for patients with inadequately controlled severe persistent IgE-dependent allergic asthma. Many publications have appeared about its use in patients who do not respond to standard therapy (30-36).

By decreasing the amount of free IgE available to interact with FcεRI on mast cells, omalizumab may essentially block the downstream cascade of asthma.

Mechanism of action

Immunoglobulin E (IgE) plays a central role in the pathophysiological cascade of allergic asthma, especially in the acute response to antigens and in the perpetuation of bronchial airway inflammation. In humans, IgE levels positively correlate with the presence of asthma symptoms, probability for allergic sensitization, Forced Expiratory Volume in the first second (FEV₁) decline, eosinophilia, emergency room (ER) visits and severe exacerbations. Given the dominant role of IgE in the pathologic features and clinical manifestations of allergic asthma, the concept that targeting IgE and blocking its function could lead to a significant clinical im-

Table 3 - Therapeutic options in severe asthma (22).

A. Conventional therapy (ICs, SABA, LABA, AntiLTs; OCs)
B. Unconventional treatment options
- Antifective
- Antifungal
- Immunomodulating agents (methotrexate, cyclosporine, azathioprine)
- Bronchial thermoplasty
C. Biologics
- Anti IgE (Omalizumab)
- Anti TNF α
- Anti IL-13
- Anti IL-5
D. Other therapies
- Long-acting anticholinergic bronchodilator
- Vasoactive intestinal peptide analogs and potassium-channel openers
- Tyrosine kinase inhibitors

ICs: inhaled corticosteroids; SABA: short acting beta2-agonists; LABA: long acting beta2-agonists; AntiLTs: leukotrien antagonists. OCs: oral corticosteroids.

provement was soon apparent and gained wide acceptance (37).

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that specifically targets and binds free IgE, preventing it from interacting with the high and low-affinity receptors, Fc ϵ RI and Fc ϵ RII. By decreasing the amount of free IgE available to interact with Fc ϵ RI on mast cells, omalizumab may essentially block the downstream cascade of asthma. As a consequence, inflammatory cells become down-regulated, so that mast cell and basophil activation and subsequent release of inflammatory mediators are inhibited (38-40). It has been also emphasized the possible role of omalizumab in affecting airway remodeling by reducing the thickening of the reticular basement membrane and eosinophil infiltration (41). Omalizumab has several effects on cellular and clinical markers of airway inflammation, as reported in Table 4.

Practical use

In patients with allergic asthma and poor disease control despite best available therapy, omalizumab as add-on therapy may reduce asthma symptoms, clinically significant asthma exacerbations, emergency visits and hospitalizations due to asthma, in clinical trials as well as in real-life settings.

Omalizumab was approved by the US Food and Drug Administration (2003), Health Canada (2005) and the European Medicines Agency (2005) for use in adult patients with moderate to severe persistent asthma who do not achieve control with inhaled corticosteroids, have a serum IgE 30-1500 (EU) or from 700 International Units (IU)·mL⁻¹, and also test positive for reactivity to a perennial airborne allergen; its use was also approved for adolescents and children over 12 years of age, and lately of over six years. In Italy, omalizumab

was approved for use in adults and children older than six years with severe allergic

asthma; for adults only, FEV₁ less than 80% of the predicted value is also required.

Omalizumab binds circulating free IgE regardless of antigen specificity, and is thereby potentially useful for atopic disorders caused by perennial allergens, and also in polysensitized patients. Unlike IgE, which has a half-life of 1-2 days in humans, omalizumab circulates similarly to human IgG1 antibodies, with a half-life of about 21 days even when it binds IgE, thus forming trimeric or hexameric complexes. Due to these pharmacokinetic properties, omalizumab is usually administered subcutaneously every 4 weeks. Shorter treatment intervals are needed when patients require relatively higher drug doses (patients requiring more than 300 mg monthly are treated every 2 weeks). After a single subcutaneous injection, omalizumab induces an 84%-99% reversible reduction of unbound serum IgE, levels which last for 4-6 weeks (31).

Clinical responses to omalizumab treatment are variable and strictly individual; they include improved asthma scores, decreased exacerbations, decreased steroid use, improved peak flows, decreased hospitalizations, and improved asthma control (30,31,42).

The INNOVATE study was the first trial to show that omalizumab is effective and should be considered as add-on therapy for patients with inadequately controlled severe persistent asthma who remained symptomatic despite best available therapy (32). 419 patients (12-75 years) inadequately controlled despite therapy with high-dose inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA) with reduced lung function and a recent history of clinically significant exacerbations were randomized to receive omalizumab or placebo for 28 weeks in a double-blind, parallel-group, multicentre study. The clinically significant asthma exacerbation rate (primary efficacy variable), was 0.68 with omalizumab and 0.91 with placebo (26% reduction) during the 28-week treatment phase (P = 0.042). Omalizumab significantly reduced the severe asthma exacerbation rate (0.24 vs 0.48, P = 0.002) and the emergency visit rate (0.24 vs 0.43, P = 0.038). Omalizumab significantly im-

Table 4 - Effects of omalizumab on cellular and clinical markers of airway inflammation (Adapted from 40).

Cellular markers

- (a) Reduces free IgE
- (b) Downregulates high-affinity FcεRI receptors on mast cells, basophils, and dendritic cells
- (c) Reduces IgE positive cells and high-affinity FcεRI receptors in bronchial submucosa
- (d) Reduces mast cell-associated interleukin-4 in bronchial submucosa
- (e) Reduces eosinophils in the blood, sputum, and tissue
- (f) Decreases IgE production

Clinical and functional markers

- (a) Reduces exhaled nitric oxide (eNO)
 - (b) Reduces histamine release
 - (c) Reduces skin prick wheal and flare reactions
-

proved asthma-related quality of life (QoL), morning Peak Expiratory Flow (PEF) and asthma symptom scores. The incidence of adverse events was similar between treatment groups.

The efficacy of omalizumab in adults, adolescents, and children with moderate-to-severe asthma has been confirmed by a recent meta-analysis of eight placebo-controlled studies published between 2001 and 2009, involving approximately 3000 patients (33). This systematic review considered reductions of steroid use and asthma exacerbations as the primary outcomes; secondary outcome measures included lung function, use of rescue medication, asthma symptoms, and health-related QoL. All data indicate the efficacy of add-on omalizumab therapy, together with an acceptable safety profile. In a further randomized, multicenter, parallel group, double blind placebo-controlled trial carried out in 850 patients (12-75 years) who had inadequately controlled asthma despite treatment with high dose of ICS and LABA, Hanania et al. have confirmed the efficacy of omalizumab (34). During 48 weeks, the rate of protocol-defined asthma exacerbations was significantly reduced with omalizumab compared to placebo (0.66 vs. 0.88 per patient; $P \leq 0.006$), representing a 25% relative reduction (incidence rate ratio, 0.75 [95% CI, 0.61 to 0.92]). Omalizumab improved mean of asthma quality of life questionnaire (AQLQ) scores (0.29 point [CI, 0.15 to 0.43]), reduced mean daily albuterol puffs (0.27 puff/d [CI, 0.49 to 0.04 puff/d]), and decreased mean asthma symptom score (0.26 [CI, 0.42 to 0.10]) compared with placebo during the 48-week study period. The incidence of adverse events (80.4% vs. 79.5%) and serious adverse events (9.3% vs. 10.5%) was similar in the omalizumab and placebo groups, respectively.

EXCELS (Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma) (35) is a prospective multicenter cohort study of 5000 individuals treated with omalizumab and 2500 control patients followed for 5 years to observe the long-term clinical safety and effectiveness of omalizumab. Differences in concomitant medication use following initiation of omalizumab were examined. Due to the large number of enrolled patients, this study provided a unique opportunity to examine concomitant medication use in "real-world" settings of omalizumab users in clin-

ical practice. For each of the common asthma medication classes examined (e.g. ICS, SABA, and LTM) the majority of patients newly treated with omalizumab were able to decrease their medication doses.

Storms et al. (36) have recently published a retrospective review comparing clinical experience with the data reported in the controlled studies. Data tracking for 167 patients progressively enrolled between 2003 and 2010 and treated with omalizumab included: symptoms, FEV₁, systemic steroid bursts, and need for short-acting bronchodilator rescue measured at the start of therapy, at 3, 6, and 12 months after starting treatment, and yearly thereafter. Asthma control improved with omalizumab over time (up to 6 years) as indicated by fewer symptoms and reduced need for rescue medication ($p \leq 0.001$ for both). FEV₁ remained stable. The number of patients reporting asthma exacerbations requiring urgent care decreased by 49% during the first 12 months of treatment ($p \leq 0.01$), and significant reductions in exacerbations were also evident when measured by hospitalizations or systemic corticosteroid bursts ($p \leq 0.001$ for both). These results support all data emerging from controlled clinical trials on severe asthma patients, showing that adding omalizumab to a patient's current therapy may significantly reduce the likelihood of asthma exacerbations, including episodes requiring urgent care (ED visits and after-hours office visits) and/or hospitalizations.

The effect of omalizumab on lung function is still under debate; nevertheless, a recent open-label study (38) performed in patients with severe uncontrolled allergic asthma randomized to receive best standard anti-asthma therapy with or without omalizumab, showed a significant increase in percentage predicted FEV₁ throughout a 1-year period of anti-IgE treatment in comparison with control values.

In conclusion, in patients with allergic asthma and poor disease control despite best available therapy, omalizumab as add-on therapy may reduce asthma symptoms, clinically significant asthma exacerbations, emergency visits and hospitalizations due to asthma, in clinical trials as well as in real-life settings. The effect of omalizumab on lung function remains controversial. Clinical and functional effects of omalizumab on asthmatic patients are reported in Table 5.

Table 5 - Clinical and functional effects of omalizumab on asthma (33).

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- A. Decreased exacerbations
 - B. Improved peak flow
 - C. Small improvement in FEV₁
 - D. Decreased rescue β 2-agonist use
 - E. Improved quality of life
 - F. Decreased mean nocturnal clinical score
 - G. Decreased total asthma clinical score
 - H. Decreased hospitalizations
 - I. Steroid-sparing effect
-

Treatment duration

Although the optimal duration of omalizumab treatment remains unclear, there is no doubt that the injections need to be continued for very long periods of time.

One major concern on omalizumab therapy refers to its duration. It is well known that either a dose reduction of omalizumab or its complete cessation leads to an increase towards baseline levels of both free serum IgE concentrations and allergen-specific skin prick test reactivity (43). In parallel, clinical observation shows that if omalizumab

treatment is interrupted for whatever reason, asthma symptoms and exacerbations relapse within a few months (44).

Nonetheless, Nopp et al. (45) have reported that 6 years-treatment with omalizumab induced durable improvement in asthma symptoms and lung function, which was maintained in the majority of patients studied for periods of 12-14 months after drug withdrawal. Indeed, three years after discontinuing treatment with omalizumab, 12 of 18 patients reported improved or unchanged asthma compared with ongoing omalizumab treatment. Most of the patients were in a stable clinical condition, 16 of 18 had no increase in nightly asthma attacks and 14 of 18 had little or no increase in medication. Considering this and the parallel downregulation in basophil allergen sensitivity, still detectable 1 year after omalizumab withdrawal, the Authors speculate that, due to the protection of omalizumab many patients might "grow out" of their allergy more quickly than otherwise. However, further studies are needed to verify whether omalizumab should be prescribed lifelong or as a relatively long-term course. Although the optimal duration of omalizumab treatment remains unclear, there is no doubt that the injections need to be continued for very long periods of time and that the ability of omalizumab to lower free IgE in serum depends on dose, patients' body weight and baseline total serum IgE level (6,45,46).

Prediction of response to therapy

At present, there are no established criteria for identifying patients who will respond to omalizumab based on pre-treatment characteristics; neither total nor specific IgE was found to have consistent predictive value for

omalizumab response. A pooled analysis of five studies found the physician's global evaluation of treatment effectiveness (GETE) following 16 weeks of omalizumab therapy to be the most meaningful measure of response (47). The physician's GETE is a composite measure that encompasses multiple aspects of evaluation of response, including patient interviews, review of medical notes, spirometry and diaries of symptoms, rescue medication use, and peak expiratory flow (PEF). Patients considered by the physician to have reached complete asthma control, or a marked improvement in their asthma control, are classified as *treatment responders*. Patients showing discernible but limited control, no appreciable change or decreasing control are classified as *treatment non responders*. Bousquet et al. (48) have recently reported the results of a randomized, open-label, parallel-group study designed to identify the persistence of treatment responders in patients receiving omalizumab (258 patients, aged 12-75) in addition to optimized asthma therapy (OAT) (91 patients in the same age group). The investigator's GETE at week 16 (the 16-week evaluation period was chosen as it is consistent with the mechanism of action of omalizumab) predicted persistence of response or non response to omalizumab at week 32 for 83.3% (215/258) of patients. OAT patients showed a lower persistence of response (18/28 [64.3%]) and a higher persistence of non response (57/63 [90.5%]) than omalizumab patients. Excellent and good GETE ratings in omalizumab-treated patients were reflected by improvements in exacerbation rates ($P < 0.001$), severe exacerbation rates ($P = 0.023$), hospitalizations ($P = 0.003$), total emergency visits ($P = 0.026$) and overall score of the Asthma Control Questionnaire (ACQ) ($P < 0.001$). They conclude that physician's GETE performed at 16 weeks is an effective predictor of continuing persistent response to omalizumab for the majority of patients. Accordingly, in clinical practice the omalizumab EU label states that only patients who have responded following an assessment at 16 weeks should continue to receive omalizumab therapy.

Patients receiving omalizumab injections show low incidence of adverse effects, mainly cutaneous ones, including site pain and bruising, warmth, erythema, swelling, and urticaria-like eruptions.

Safety

Overall, omalizumab has a favorable safety profile and no serious adverse effects have appeared consistently in asthmatic patients undergoing this treatment. Reactions occurring fairly frequently in patients receiving omalizumab injections include site pain and bruising, warmth, erythema, swelling, and urticaria-like eruptions. The local injection site reactions are sometimes severe (in up to 12% of the injections). Other adverse effects include bronchospasm, hypotension and syncope, urticaria, and/or angioedema (31). Post marketing studies have reported less than 0.2% of anaphylactic reactions, occurring mainly (60%) in the first 2 hours (49). Therefore it is recommended that omalizumab should be administered in specialist centers and under medical supervision.

Table 6 - Adverse events with omalizumab (personal data).

Reaction/AE	Frequency (per 100 patients)	Frequency (per 100 injection)	Notes
Cutaneous			
Injection site reaction	50	40	warmth, erythema bruising, burning
Skin eruption	7	0.1	dermatitis, urticaria
Gastro-intestinal			
Nausea	3.5	0.1	
CNS			
Headache	10.7	0.2	

In our clinical experience, consecutive patients with severe asthma treated with omalizumab showed functional and clinical improvement, but no of them needed to suspend omalizumab administration because of major adverse events. Among our 28 adult patients treated with omalizumab from 2010 to 2012, we observed an incidence of systemic adverse reactions less than one percent (Table 6).

The clinical randomized trial published by Hanania et al. (34) reported a similar incidence of adverse events in the omalizumab group and the placebo group (80.4% vs.79.5%, respectively). Serious adverse events were also similar in the two groups (9.3% vs. 10.5%). The rate of adverse events of special interest (including anaphylaxis, cancer, urticaria, hypersensitivity reactions, thrombocytopenia, injection-site reaction, and bleeding-related disorders) was also similar in the two groups. The risk of malignancy has also been a safety concern with omalizumab. Recent pooled data (50) from 67 phase I to IV clinical trials including 11459 patients (7789 received omalizumab and 3178 received placebo) demonstrated no association between omalizumab treatment and risk of malignancy; in fact, the ratio of the incidence of malignancy in the omalizumab group compared with the placebo group was lower. Furthermore, interim results from the EXCELS study (Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma) showed no increased risk of malignancy with omalizumab after long-term use (35,51).

Conclusion

Although clinical response to treatment is variable and strictly individual, the anti-IgE monoclonal humanized antibody omalizumab can be considered a valid option as add-on therapy for patients with severe persistent allergic asthma inadequately controlled by conventional drug treatment, as it has demonstrated important improvements in respiratory symptoms and QoL, with a reduction of asthma exacerbations, emergency room visits, and use of systemic corticosteroids and rescue bronchodilators. However, some theoretical and practical aspects of anti-IgE therapy in bronchial asthma need more research. There is a compelling need for a tool to objectively assess response to treatment; in addition, a clinically measurable biomarker is essential, which may be

used as a predictor of response to anti-IgE treatment, especially in the long term.

A relevant question remains whether such therapy is effective even in patients with IgE levels below or above the recommended range. Moreover, although patients with non-atopic (intrinsic) severe asthma are currently excluded, there is evidence of local IgE production in the airways of some of these difficult-to-treat asthmatic patients (52); based on this consideration, it could be important that future studies define the drug's role for this specific category of patients.

There is also a need for studies focusing on the effect of omalizumab as pretreatment for patients with persistent allergic asthma who are candidates for allergen immunotherapy, in order to reduce the rate of systemic reactions to specific immunotherapy (SIT) and improve its tolerability.

Finally, also investigations on optimal duration of treatment, effect on IgE modulation, airways inflammation and remodelling should be encouraged to better understand the potential of omalizumab therapy for allergic severe asthma.

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