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Review Article

Severe Uncontrolled Allergic Asthma: The Use of Omalizumab in Routine Care

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Abstract

Our improved theoretical understanding of IgE-mediated immediate-type allergic diseases has led to an important step forward in treating patients suffering from severe uncontrolled asthma – a major global health problem. In 2005, omalizumab (Xolair®), a humanized anti-IgE antibody received approval for the treatment of (moderate-to-) severe persistent asthma. Omalizumab interferes with the allergic cascade by binding free serum IgE, blocking the interaction of IgE with basophils or mast cells.

We conducted a systematic review of published research that assessed the mode of action, clinical indications, dose and safety of omalizumab. Furthermore, we reviewed the May 2014 GINA guideline, which suggests anti-immunoglobulin E treatment with omalizumab as preferred controller treatment for patients with moderate or severe allergic asthma that is uncontrolled on step 4 treatment.

We present available evidence for indications and practical application of omalizumab for achieving asthma control in these patients. As an add-on therapy, omalizumab has been proven clinically effective and safe in numerous randomized controlled trials and real-life surveys. Omalizumab reduces asthma exacerbations, improves symptoms and quality of life. Based on more than 9 years of scientific evidence and clinical experience, practical considerations for omalizumab use for the specialists are detailed. In clinical practice, pulmonologists and allergy specialists can easily integrate IgE blockade with omalizumab into their routine care for the long-term treatment of allergic asthmatics inadequately controlled with GINA treatment step 4.

Keywords: Anti-IgE Antibody; Immunological Cascade; Severe Uncontrolled Asthma; Atopy; Allergic (IgE-mediated) Asthma; Omalizumab

Abbreviations

ABPA: Allergic Bronchopulmonary Aspergillosis;
ACQ: Asthma Control Questionnaire;
ACT: Asthma Control Test;
AE: Adverse event;
ATS: American Thoracic Society ;
csU: Chronic spontaneous urticarial;
EPR: Expert Panel Report;
ERS: European Respiratory Society ;
FDA: Food and Drug Administration;
FEV1: Forced Expiratory Volume in 1s ;
GCP: Good Clinical Practice;
GETE: Global Evaluation of Treatment Effectiveness;
GINA: Global Initiative for Asthma;

ICS: Inhaled Corticosteroid;
LABA: Long-Acting Beta 2-Agonist;
LAR: Late-Phase Allergic Response;
LTRA: Leukotriene Receptor Antagonist;
LTs: Leukotrienes;
NAEPP: National Asthma Education and Prevention Program;
EPR-3: Expert Panel Report 3 (NAEPP);
OCS: Oral Corticosteroid;
PEF: Peak Expiratory Flow;
QOL: Quality of Life;
RCT: Randomized Controlled Trial;
SABA: Short-Acting Beta 2-Agonist;
s.c.: Subcutaneous Injection;
theoph: Theophylline;
Th2: T Helper Cell type 2

Introduction

Allergic reactions are triggered by allergens that invade the body via the respiratory tract, gastrointestinal tract or the skin. These allergens are taken up by antigen-presenting cells like dendritic cells that activate lymphocytes, inducing specific IgE production and binding the latter to high-affinity IgE receptors (FcεR1) on resident mast cells or basophils [1]. After re-exposure, the allergen interacts with cell membrane-bound specific IgE, triggering activation of the allergic cascade as illustrated in Figure 1.

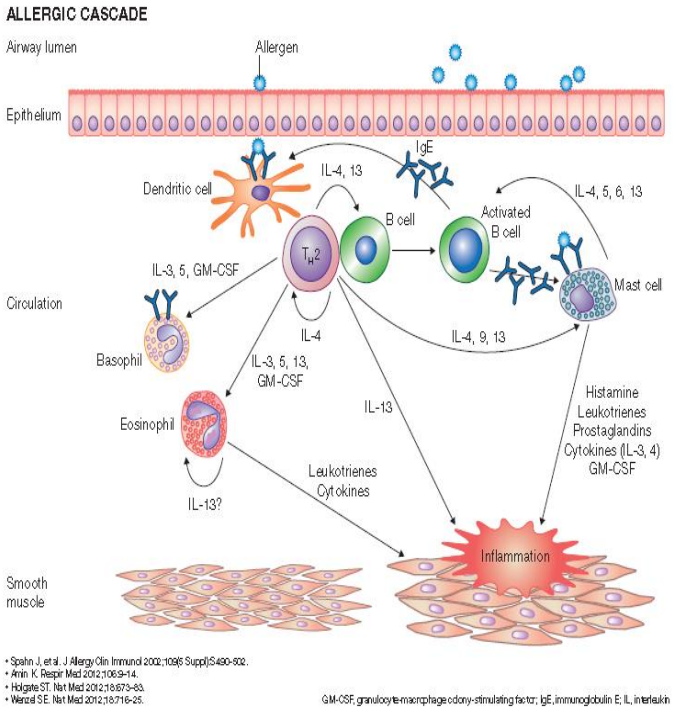

Figure 1. The allergic cascade.
After allergen exposure, DC take up allergens and present the processed antigens to B-cells and T-cells, activating IgE production in Th2 cells. IgE binds to FCepsilon receptors on mast cells and basophils. After re-exposure, allergens crosslink IgE-molecules bound to the receptors leading to degranulation and release of proinflammatory cytokines and other mediators. These trigger clinical symptoms.

During IgE-mediated type 1 allergic reactions, histamine and other preformed inflammatory mediator compounds are released from activated mast cells. Histamine stimulates H1-receptors, thereby contributing to the early allergic reaction, causing the clinical symptoms of redness, swelling, itching, sneezing, runny nose, nasal congestion and red eyes, a syndrome called allergic rhinoconjunctivitis. Other clinical expressions include bronchial spasm, wheezing, dyspnea, chest tightness, and cough, termed allergic asthma. After 6 – 12 hours, the newly synthesized mediators in the arachidonic acid cascade, such as leukotrienes, can trigger a Late-Phase Allergic Response (LAR) [2].

Continuous or repeated allergen exposure can lead to persistent inflammation [3,4]. This chronic allergic inflammation causes mucosal infiltration by inflammatory cells, mucus hypersecretion, basement membrane fibrosis, smooth muscle hypertrophy, alterations of angiogenesis and other structural changes that are linked to airway remodeling.

Despite our improved scientific understanding of these complexly intertwined mechanisms, the clinical practitioner continues to be faced with serious allergic diseases like asthma, especially in its most severe form [5].

Different asthma phenotypes

Nowadays, "asthma" is merely an umbrella term, counting several different phenotypes [6,7]. In May 2014, GINA introduced a new definition of asthma, stating for the first time that asthma is a heterogeneous disease [8].

Phenotyping (and endotyping, i.e. determining important pathophysiological characteristics) asthma has important consequences according to pharmacotherapy, with steadily increasing importance. Classical asthma phenotypes are:

Allergic (extrinsic) asthma is the standard nomenclature used to describe asthma resulting from immunological reactions, primarily mediated by immunoglobulin E (IgE)-dependent processes with high Th2 (T helper cell type 2) mediated eosinophilic inflammation [6]. Allergies are the strongest predisposing factor for the development of asthma in children and adolescents and are the primary cause about two thirds of adults, making allergic asthma the most common type of asthma [9-11]. Allergens that can trigger asthmatic responses can be seasonal (e.g. grass or tree pollen) or perennial (e.g. house dust mite, animal dander or mold spores). Occupational expo-

sure to allergens also has to be considered.

Nonallergic (intrinsic) asthma is described by Johansson et al. as: "*The mechanisms initiating nonallergic asthma are not well defined, although similar inflammatory changes occur in both forms of asthma* [12]". Indeed, several similarities have been found between allergic and nonallergic asthma [10,11]. Nonallergic asthma commonly starts later in life (late onset asthma) and is often triggered by respiratory infections. By definition, causative allergies or circulating IgE antibodies to environmental allergens are not detectable in nonallergic asthma [13]. Despite this, local IgE production is discussed [14-19]. Some studies have shown that up to 25% of adult asthmatics are nonallergic [20,21] and that adults with nonallergic asthma often suffer from a more severe form than allergics [10,22]. In contrast, in children, the prognosis is more severe in allergic versus nonallergic asthma patients [23].

Mixed phenotypes of asthma are also possible. Particularly during the course of an initially allergic asthma, in subsequent years in adulthood, other components may become clinically prominent.

Given these common clinical features, allergy tests (prick, specific IgE, occasionally provocation tests) are needed for the differential diagnosis [10,24]. Identifying allergic and mixed phenotypes is not only clinically meaningful for prognostic purposes, but to identify patients who benefit significantly from specific allergen immunotherapy [25] or anti-IgE antibody therapy [26].

New Asthma phenotypes

The above mentioned "classical" asthma phenotypes are characterized by Th2 (eosinophilic) inflammation, IgE mediated allergic or non-IgE mediated (non-allergic but eosinophilic) endotypes, e.g. the phenotype of late onset eosinophilic asthma [6]. Late onset eosinophilic asthma patients might respond to new, experimental anti IL-5 and IL-13 antibodies [27,28].

Other asthma patients have a low Th2 (non-eosinophilic but neutrophilic) inflammation endotype responding poorly to corticosteroids [7,29]. The paucigranulocytic asthmatic endotype is a further poor corticosteroid responder. As yet, no well-established treatments are available for the neutrophil and paucigranulocytic endotypes [6].

Further asthma phenotypes, i.e. obesity related asthma, exercise induced bronchospasm and asthma with fixed airflow limitation emerge, but as yet the terminology and characterization of these phenotypes are not final (Table 1) [8].

Table 1. Some Asthma phenotypes and their endotypes [6,8].

Asthma phenotype	Endotype
Early onset allergic	High Th2 (eosinophilic) IgE Mediated
Late onset eosinophilic/non-allergic	eosinophilic non-IgE mediated often with sinusitis
Fixed airflow limitation	Low Th2 (neutrophilic) Airway wall remodelled
Obesity related late onset, female	Paucigranulocytic
Exercise induced bronchospasm	Mast cell mediator release

Definition of asthma severity

Older guidelines assessed asthma severity based on the level of symptoms, airflow limitation and lung function variability before treatment. According to GINA 2005, untreated asthma can be referred to as either intermittent or persistent at a mild, moderate or severe level [30]. This initial severity classification was used to determine the appropriate asthma treatment. While two-thirds of asthma patients in the population have intermittent asthma, one-third suffers from persistent asthma [31]. However, this asthma severity concept is now outdated and GINA 2014 doesn't refer to it anymore. Many patients formerly characterized and treated as severe asthma patients can be controlled with low dose ICS treatment.

Clinically more important than severity before treatment is the individual answer of the patient to asthma therapy, which is orientated towards achieving the best possible asthma control [32]. New guidelines therefore introduced the concept of treatment steps that is, the medication required to achieve asthma control [33]. The new ERS/ATS guidelines define severe asthma as follows: "*When the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy* [34]."

The differential diagnosis should confirm the diagnosis of severe asthma by excluding both asthma mimicking conditions and asthma aggravation comorbidities, summarized in Table 2. Furthermore, compliance factors [35], inadequate inhaler technique [36], persistent allergen exposure, and smoking [37] can be responsible for poor asthma control. Figure 2 illustrates a diagnostic algorithm.

Table 2. Asthma aggravation comorbidities and conditions that may mimic severe asthma [34,111,112].

Asthma mimicking conditions:	Asthma aggravating comorbidities:
• COPD	• Gastroesophageal reflux disease
• Vocal cord dysfunction	• Obesity
• Dyspnea on exertion	• Chronic rhinosinusitis
• Bronchiolitis	• Immunodeficiency
• Recurrent pulmonary embolism	• Allergic bronchopulmonary aspergillosis (ABPA)
• Tuberculosis	• Behavioral and panic disorders
• Cardiac failure	• Depression
• Cystic Fibrosis	
• Ciliary dyskinesia	
• Churg-Strauss syndrome	
• Hypereosinophilic syndromes	

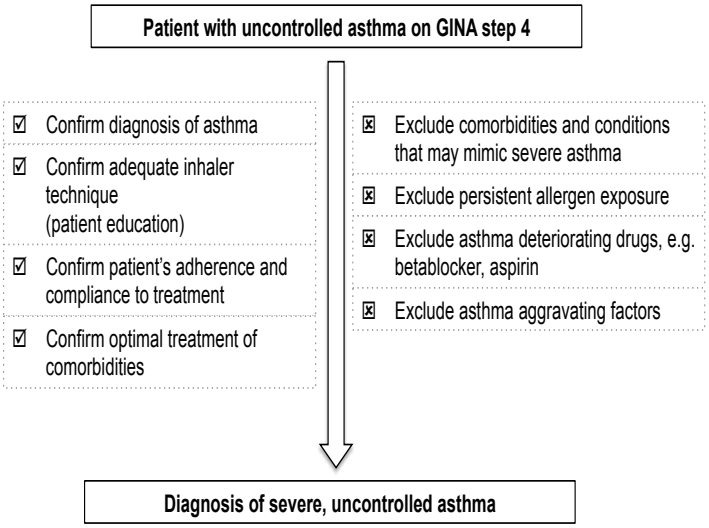

Figure 2. Algorithm to diagnose severe uncontrolled asthma [34,111,113,114] .

Stepwise asthma therapies and disease control

In lieu 2007 GINA guidelines introduced the new paradigm of the concept of asthma control according to day and night symptoms, activity limitations, reliever use, exacerbations and lung function over a period of 4 weeks [30].

Table 3 shows criteria for controlled, partly controlled and uncontrolled asthma. A single exacerbation defines asthma as uncontrolled for a week duration and should prompt review of maintenance treatment. GINA directly links asthma control to decisions about asthma treatment: A stepwise pharmacotherapeutic approach with 5 treatment steps has been introduced with a recommendation that treatment should be increased or decreased according to the asthma control status. Figure 3 shows the new GINA treatment recommendations for asthma control.

Table 3. GINA 2014 assessment of asthma control [8].

Asthma Symptom Control	Level of Asthma Control		
In the past 4 weeks, has the patient had:	well controlled	partly controlled	un-controlled
• Daytime asthma symptoms more than twice a week? • Any night waking due to asthma? • Reliever needed for symptoms more than twice a week? • Any activity limitation due to asthma?	None of these	1 – 2 of these	3 – 4 of these

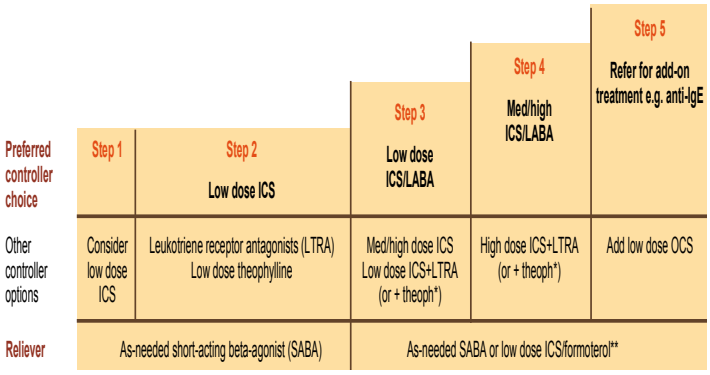

Figure 3. Stepwise approach to controlling asthma.
Modified from GINA 2014[8]8
*for children 6-11 years, theophylline is not recommended, and the preferred step 3 treatment is medium dose ICS.
**low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.

GINA Step 1:

Asthma patients free of symptoms only occasionally need short-acting beta2-agonist (SABA) rescue medication (no more than twice a week). These patients do not need controller treatment. However, if they are at risk for asthma exacerbations, low dose ICS controller therapy should be considered.

GINA Steps 2–5:

Beyond rescue medication, these patients need regular controller treatment. Since asthma is a disorder characterized by ongoing inflammatory processes in the airway submucosa, inhaled corticosteroids (ICS) are the preferred controller choice for asthma. Regular anti-inflammatory treatment is

needed to lower the risk of exacerbations and chronic morbidity. ICS are effective in improving asthma control in both children and adults, but they do not appear to cure the disease [38-40]. Additionally, the dose-response relationship is flat and a plateau in efficacy is seen with increasing doses of ICS [41,42].

GINA Step 2:

Preferred controller choice: low doses ICS
Alternative controller choice: Leukotriene receptor antagonists (LTRA) or low dose theophylline

GINA Step 3:

Preferred controller choice: low dose ICS plus LABA
Alternative controller choice: Medium to high dose ICS or low dose ICS plus LTRA (or plus theophylline). However, for children 6-11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium dose ICS
In the May 2014 update, GINA added low dose fixed ICS/formoterol combinations as recommended reliever treatment beyond SABA on step 3-5 of asthma treatment.

GINA Step 4:

Preferred controller choice: Medium to high dose ICS plus LABA
Alternative controller choice: High dose ICS plus LTRA (or plus theophylline – but not for children, see above)

GINA Step 5:

Preferred controller choice for allergic asthma: add-on therapy, e.g. omalizumab (if indicated, only for allergic asthma)
Alternative controller choice: e.g. low dose OCS

Based on a large body of literature published in the past decade, GINA changed the preferred controller for allergic asthma moving directly to omalizumab. Low dose OCS remains only the alternative choice for allergic asthma. If the indication for omalizumab (allergic asthma) is not met, alternative controller options like long-term low dose (up to 7.5mg) systemic steroids should be introduced on step 5. If possible, high-dose systemically administered steroids should only be applied to treat exacerbations – chronic use of high-dose systemic corticosteroids should be avoided, due to severe side-effects [43,44]. Patient should be counselled about potential side-effects. They should be regularly monitored for risk of corticosteroid-induced osteoporosis and where appropriate treated with preventive therapy [8,43,44].

In the future, further phenotype-specific treatments might be available for step 5 controller options.

The practical health care challenges grow with increasing disease severity and the difficulties of disease control. The most challenging population can be said to be the 5% of severe asthmatics who remain inadequately controlled despite guideline-compliant, optimized therapy with ICS and LABA [8,32,34,45]. They are at high risk of severe exacerbations, hospitalizations and mortality [46,47]. This minority represents the asthma population with the most severe disease, but at this time with the fewest additional therapeutic options and therefore the greatest unmet medical need [45].

Treatment of severe uncontrolled allergic asthma

For asthma not adequately controlled by conventional treatment strategies (preferred treatment: high dose ICS+LABA), pharmacotherapies using biologics that target different aspects of airway inflammation are being developed to help patients with persistent asthma symptoms achieve control [48]. In this regard, add-on anti-IgE treatment (omalizumab) is the first and at this time the only established option for treatment of severe uncontrolled allergic asthma [8,49]. If a patient is not eligible for omalizumab therapy, other drugs beyond OCS that could be efficient, include anticholinergics as add-on therapy [8,50]. Experimental drugs, including methotrexate, cyclosporine, platinum salts, gold or troleandomycin do not have an acceptable risk-benefit ratio and are therefore not recommended by current guidelines.

Omalizumab – a safe and effective add-on option for severe uncontrolled allergic asthma

In 2003, omalizumab, a humanized anti-IgE antibody (Xolair®, Genentech and Novartis) became available in the USA and Australia for managing chronic allergic asthma with a sensitization to a perennial aeroallergen. Since then, Omalizumab has also been approved in many further countries, including European Union, Russia, Japan, Switzerland and Canada.

Omalizumab targets the Cε3 epitope on the fragment of free circulating serum IgE preventing binding the α chain of the high-affinity trimeric IgE receptor on FcεRI-bearing cells. IgE is a key component of allergic asthma pathophysiology and contributes to both the early- and late-phase inflammatory cascade of the airways [51]. Reduction in surface-bound IgE on FcεRI-bearing cells by omalizumab inhibits allergen-induced activation of mast cells and limits the degree of release of mediators of the allergic response. By this mechanism, omalizumab blocks the allergic cascade at a very early stage. Treatment with omalizumab also reduces the number of FcεRI IgE receptors on dendritic cells, basophils and mast cells in atopic patients [52,53].

Figure 4 illustrates how IgE blockade by omalizumab interferes in the allergic cascade and thereby reduces or controls

the clinical effects of asthma.

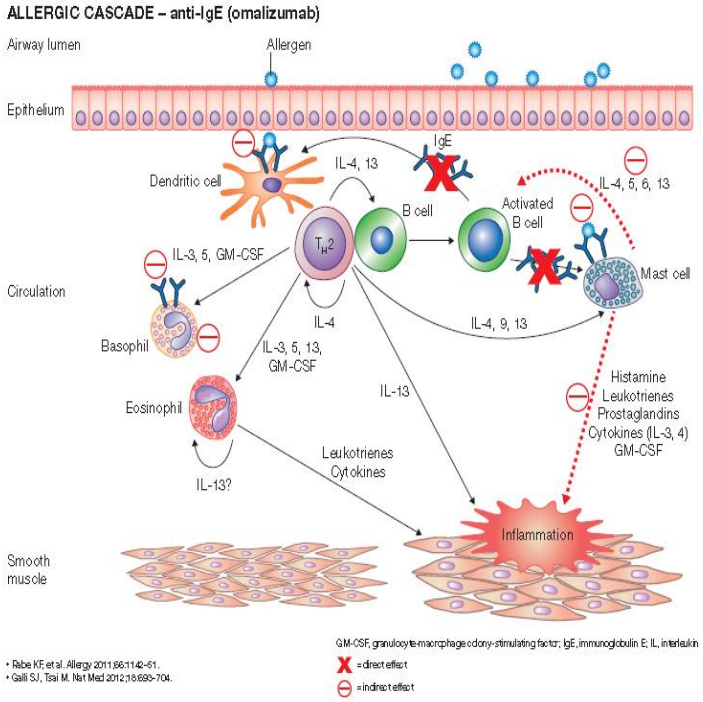

Figure 4. Allergic cascade – anti-IgE (omalizumab).
How omalizumab stops the allergic cascade by IgE blockade to control the clinical effects of asthma. Omalizumab blocks free serum IgE, and thereby also reduces FCεRI-expression. This leads to a reduction of tissue infiltration of immune cells and consequently, a reduction in clinical symptoms.

According to its approval, omalizumab is indicated in the USA 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 inhaled corticosteroids [54].

In the EU, Omalizumab is indicated as add-on therapy to improve asthma control in patients (6 years of age and above) 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 (FEV_1 <80%, in adults and adolescents ≥12 years of age only) 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 [55]. Moreover, unequivocal *in vitro* reactivity to a perennial aeroallergen is required if total IgE <76 IU/ml (or for children in the EU 6 to <12 years of age IgE <200 IU/ml). In addition to the differences in the approved indication, there are also some differences in the dosing regimens (see Dosing).

Proven clinical efficiency of omalizumab

Numerous randomized double-blind placebo-controlled studies including adult and adolescent patients were conducted to demonstrate the efficacy and safety of omalizumab as add-on therapy in the treatment of severe uncontrolled allergic asthma. Duration of exposure ranged from six months to more than one year [26, 56-61]. In the pivotal efficacy randomized controlled trials, omalizumab has demonstrated to safely reduce the incidence of asthma exacerbations, severe asthma exacerbations and emergency visits. Adding omalizumab to different treatment regimens showed significant improvements in the following outcomes:

- Asthma exacerbations [26,58,59,62,63]
- Corticosteroid burden [58,59,62,64,65]
- Seasonal exacerbation risks in spring and autumn [62]
- Daytime symptoms[59,60]
- Nocturnal clinical symptom score[59,60]
- Rescue medication use [58-60, 65]
- Quality of life [26,58,63]
- Investigator and patient global evaluation of treatment effectiveness (GETE) [26,66]
- Morning PEF [26,58,59]

Importantly, new evidence suggests, that omalizumab prevents remodeling in chronic allergic asthma (see also Duration of successful therapy) [67,68].

Efficacy in randomized controlled trials has restricted external validity. Therefore, clinical efficacy of add-on omalizumab has also been analyzed in at least 8 separate multicenter studies. These studies assessed asthma control under real-life practice conditions conducted throughout the world on over 8,672 patients with inadequately controlled moderate to severe allergic asthma [69-79]. The periods of observation and analysis ranged from 6 months to 5 years. The centers were located throughout Central Europe, Scandinavia, Asia Minor and North America. Data were collected in a broad range of unselected asthma patients fulfilling prescription criteria.

Based on this robust real-life evidence, omalizumab demonstrated the same outcomes and the same beneficial effects as shown in the randomized controlled clinical trials: reductions in the number of exacerbations [57,59,69,70,72-78,80,81], daily doses of oral, intravenous and inhaled corticosteroids and other rescue medicines [69,72,74-78] and reductions in unscheduled hospitalizations, emergency room services and outpatient clinical visits [70,73-75]. These studies also confirmed improvements in asthma control [71,72,77,81], lung function[72,76,77] and showed even higher responder rates, if compared with RCT's [76]. Also patient-related outcomes assessed by ACQ or GETE showed better improvement in quality of life and work-related items

than the data from the clinical trials had indicated [69,76].

Practical use: dosing, application, assessment periods, patient education, precautions

Dosing

The dosing of omalizumab is calculated based on the patient's baseline serum IgE level and body weight as stipulated in the standardized tables for the applicable prescribing information (Table 4 and Table 5). IgE levels from 30–700 UI/ml in the US and 30–1500 IU/ml in the EU are approved. These are the respective levels which can be blocked by the approved maximum omalizumab monthly doses of 750mg (USA) and 1200mg (EU). For efficacy, a sufficient amount of omalizumab is needed to bind most of the free serum IgE. For serum volume, body weight was substituted as a surrogate. It was calculated that 0.016 mg/kg of omalizumab is needed per IU/ml IgE per 4 weeks. Thus, according to the IgE level and respective body weight, some patients cannot be treated on label if they exceed the approved maximum monthly dose.

Table 4. Omalizumab dosing in the EU [55].
Milligrams per dose administered by s.c. injection every 4 and every 2 weeks for adults, adolescents and children (6 to <12 years of age).

Baseline IgE - (IU/ml)	Body Weight (kg)									
	20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	150	150	150	150	150	300	300
>100-200	150	150	150	300	300	300	300	300	450	600
>200-300	150	150	225	300	300	450	450	450	600	375
>300-400	225	225	300	450	450	450	600	600	450	525
>400-500	225	300	450	450	600	600	375	375	525	600
>500-600	300	300	450	600	600	375	450	450	600	
>600-700	300	225	450	600	375	450	450	525		
>700-800	225	225	300	375	450	450	525	600		
>800-900	225	225	300	375	450	525	600			
>900-1000	225	300	375	450	525	600				
>1000-1100	225	300	375	450	**600**					
>1100-1200	300	300	450	525	**600**					
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

DO NOT ADMINISTER
data not available for dose recommendation

It is crucial for successful asthma therapy with omalizumab to reduce IgE levels sufficiently, as even a relatively small proportion of excess free IgE can still stimulate mast cells and basophils to release histamine and prime the arachidonic acid cascade [82,83]. This might explain a limited therapeutic effect in underdosed patients in non-interventional studies [75] and re-emerging symptoms after treatment cessation [84].

Table 5. Omalizumab dosing in the USA [54].
Milligrams per dose administered by s.c. injection every 4 and every 2 weeks for adults and adolescents 12 years of age and older

Pre-treatment Serum IgE (IU/ml)	Body Weight (kg)			
	30-60	>60-70	>70-90	>90-150
≥30-100	150	150	150	300
>100-200	300	300	300	225
>200-300	300	225	225	300
>300-400	225	225	300	
>400-500	300	300	375	
>500-600	300	375	DO NOT DOSE	
>600-700	375			

Key: Light blue: every 4 weeks green: every 2 weeks, IU: International Units; EU: European Union, USA: United States of America; IgE: Immunoglobulin E; s.c. injection: subcutaneous injection

How to establish the correct long-term omalizumab dose?

Prior to administration of the initial dose, the total IgE level has to be determined by commercial serum IgE assay and the patient's weight also has to be considered.

Application

Some countries are supplied with the powdered formulation of omalizumab, with each vial of omalizumab containing 150mg of the drug and requiring reconstitution prior to administration. After the diluent has been added to the vial, cautious swirling is necessary to dissolve it completely. In other countries (mostly in Europe) prefilled syringes are available with 75mg and 150mg omalizumab. However, aspiration is not possible with these syringes. Omalizumab is carefully injected subcutaneously into the deltoid region of the upper arm or, alternatively, into the upper legs. When the dose exceeds 150mg, injections should be divided and administered into both arms. The syringe should be held at an oblique angle. Avoid drops on the needle as they might cause a burning sensation.

If only 150mg doses are available but the calculated dose according to the dosing table is 225mg some specialists will round up the dose for 150mg aliquots and round down the next one, avoiding wasting 75mg omalizumab at each injection. By contrast, exact dosing is possible in countries where prefilled syringes are available in both 75mg and 150mg.

Assessment and patient education

Beyond pharmacotherapy, including omalizumab if indicated,

severe uncontrolled asthma patients also need a written action plan and patient education, which has also proven to be cost-effective [38,85,86]. Self-monitoring can also improve asthma outcomes and help practitioners monitor both effectiveness and treatment compliance and therefore should be promoted [8,38]. Particularly, omalizumab patients suffering from severe uncontrolled asthma should monitor their peak flow and their symptoms. Patient information materials are available on several websites (see Highlights Box).

Once IgE is suppressed, the onset of a clinical, beneficial response is usually delayed because the physiologic system takes time to readjust to the changed steady-state levels of IgE [26,84,87]. Consistent with this, asthma studies and clinical trials have shown that at least 12 to 16 weeks of treatment are needed before the full therapeutic response of omalizumab can be assessed for effectiveness and clinical benefit. Therefore, the clinical response should not be evaluated until 16 weeks after initiation before justifying its continuation [54,55, 90]. In the case of non-responders, diagnosis, adherence to baseline therapy and dosing should be re-evaluated and therapy optimized accordingly. Final judgment as to whether treatment is successful can sometimes only be made as late as one year after treatment has started (Figure 5) [72,88].

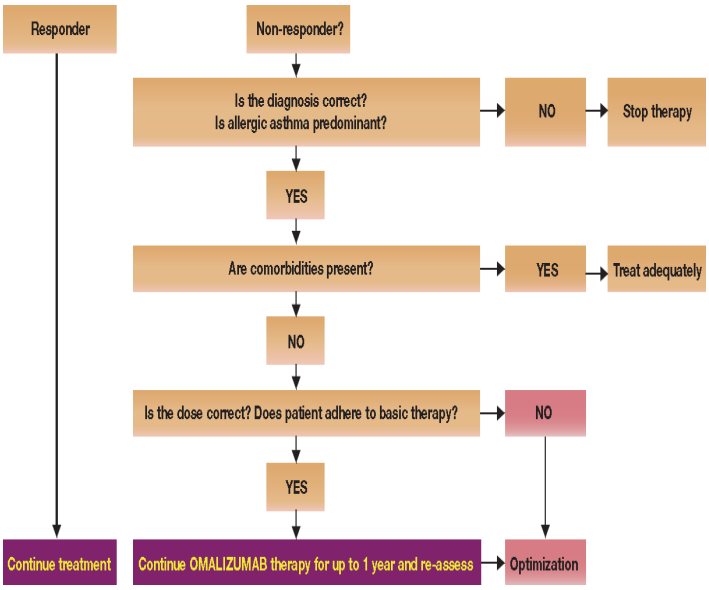

Figure 5. Reassessment of patients on omalizumab after 16 weeks of therapy [9,54,55](personal communication Kroegel 2012).

How and when to measure IgE?

Dosing of omalizumab selected according to the dosing table is based on serum total IgE measurement taken before initiating treatment. However, measuring IgE levels under omalizumab is misleading due to formation of stable IgE/anti-IgE complexes [54,55,89-91].

Transport, storage and use

Table 6 provides general instructions on how to transport, store and prepare the omalizumab lyophilized powder (available in the USA [54]) and pre-filled syringe (available in the EU [55]).

Table 6. General summarized instructions on omalizumab transportation, storage and preparation [54, 55].

	Powder (available in USA)	Pre-filled syringe (available in the EU)
Transport	At controlled ambient temperature (≤ 30°C [≤ 86°F]) by the shortest transit routes	At 2–8°C
Storage	At 2–8°C (36–46°F)	At 2–8°C
Preparation for use	• Warm to room temperature (RT) 30min before use • Use within 8 hours after reconstitution when stored in the vial at 2–8°C (36–46°F) or within 4 hours of reconstitution when stored at RT • Protect reconstituted powdered omalizumab vials from direct sunlight	• Warm to room temperature 30 min before use • Use at the latest 4 hours after removal from refrigerator
Injection	• Withdraw all of product from vial before expelling air. • De-airing: Do not leave any drops on needle	• De-airing: Do not leave any drops on needle. • Aspiration not possible

Side effects

As pooled analyses have shown omalizumab is a very safe, albeit relatively new drug [92]. In clinical trials, adverse events were on the placebo level [49,56,58,93]. The adverse events of special interest observed in clinical trials will be addressed in the following.

1. Anaphylaxis

Anaphylaxis was observed on omalizumab, but much less frequently at a rate of 0.2 [93] which is much lower than with other biologicals and has been stable for years [92]. Nevertheless, anaphylaxis can occur and appropriate precautions should be taken to counteract it. Most of the reactions observed occurred within 2 hours after the first and subsequent injections. Appropriately skilled staff and equipment for treating anaphylactic reactions must be available [54-55]. As usual, patients should be informed about the benefits and risk of treatment. After each of the first 3 injections, the patient should stay at the office for 2 hours under observation to ensure that the dose is well tolerated and that no immediate adverse events occur. Thereafter, an observation period of 30 minutes should be sufficient (similar to immunotherapy).

2. Helminthes infestation

Parasitic helminthes infestation induces production of protective IgE providing the possibility that omalizumab may increase susceptibility to helminthes infestation. Clinical data showed slightly higher rates (albeit not significant) of infestation incidences in patients at high risk [94]. Therefore, caution may be warranted in patients at high risk of helminthes infestation, in particular when travelling to areas where infestations are endemic.

3. Malignancy

In the past, there has been a numeric imbalance of tumor incidence in early clinical studies. However, a higher risk of malignant neoplasms under omalizumab could not be verified in further analyses of larger clinical data sets. Reviews by expert oncologists showed that the malignant neoplasms observed during pivotal trials with omalizumab were of varying types and most likely pre-existent, thereby rendering any causal connection to omalizumab treatment unlikely [95]. Moreover, in a large open-label safety study with 5,007 omalizumab-treated patients and 2,829 controls followed for 5 years (18,426 person-years), the incidence of malignancies was similar in the omalizumab and non-omalizumab cohorts [96]. Therefore, accumulated data from the open-label safety study, an extensive review of clinical data, a meta-analysis of all patients treated in trials, as well as the report from the expert panel, are reassuring: the relative risk of malignancy in omalizumab treated patients is not significantly higher than for asthma patients in general [92-97]. As a result, the EMA decided to remove malignancies from the product information [98].

Duration of successful therapy

Thus far, no data are available on how long successful therapy should last. Omalizumab therapy was designed as a lifelong controller therapy. However, some evidence exists that it may even have disease modifying effects [67,68,89,99-101]. Several options have been attempted at stopping therapy in practice, but no concrete experience or data have been published to date; there are anecdotal reports, however, of single cases of patients stopping at once, prolonging intervals and reducing their dose resulting in both positive and negative outcomes [84,99,100]. In Germany, an expert consensus meeting has evaluated this topic and does not recommend treatment cessation in general due to the lack of data [102].

If cessations of successful treatment are attempted after several years, the physician should carefully assess the exacerbation risk. If the therapy is stopped, the patient should still keep a diary for at least 4 months while being closely monitored, and then re-evaluated to determine whether the treatment should be reintroduced.

A retrospective study (X-TEND) published on ERS 2012, which evaluated patients from past observational studies who are still receiving omalizumab therapy or have meanwhile discontinued, showed that symptoms and disease status worsened more in patients with <3 years of omalizumab exposure. Patients with >3 years of omalizumab exposure did not change, or showed very little change compared to the end of the former observational studies. However, symptoms and asthma control were not reduced to the same extent as before starting treatment [103]. Another study published at the ERS showed that the longer patients were treated with omalizumab the less likely patients were to lose asthma control.

Omalizumab for other indications

In 2014, Omalizumab was approved by the European Commission and the US Food and Drug Administration (FDA) as add-on therapy for chronic spontaneous urticaria (csU) in adult and adolescent patients 12 years and above with inadequate response to H1-antihistamines. Further, Xolair has been approved for the treatment of csU in the several other countries, including Egypt, Turkey, Guatemala, El Salvador, Bangladesh, Pakistan, Ecuador and the Philippines. Regulatory reviews are currently ongoing in further countries including Canada, Australia and Switzerland.

Three pivotal phase III studies, ASTERIA I, ASTERIA II and GLACIAL, evaluated the efficacy and safety of Xolair in nearly 1,000 csU patients not responding to antihistamines [106-106].

ASTERIA I and ASTERIA II were global, multi-center, randomized double-blind studies that evaluated the efficacy and safety of Xolair 75mg, 150mg or 300mg compared to placebo in 323 and 318 moderate to severe csU patients respectively. In the ASTERIA II study, 44% of patients receiving Xolair 300mg were itch- and hive-free after 12 weeks of treatment ($p<0.0001$) [104]. In the ASTERIA I study, Xolair-treated patients experienced a rapid reduction in itch and hives as early as Week 1, with the therapeutic benefit sustained over 24 weeks of active treatment ($p<0.0001$)[106].

GLACIAL was a 40-week, global, multi-center, randomized double-blind study that evaluated the safety and efficacy of Xolair 300mg compared to placebo over 24 weeks [105]. It involved 335 patients aged between 12 and 75 with moderate to severe csU despite receiving standard-of-care therapy, consisting of concomitant H1-antihistamine therapy (up to four times the approved dose) and other background medications including H2-antihistamines and/or LTRAs. Patient response in GLACIAL was similar to that seen in ASTERIA I and II, lead-

ing to elimination or suppression of symptoms to minimal levels within 2 weeks of the start of treatment, and sustained throughout the 24 week treatment period [104-106].

Discussion

Unraveling the complexly intertwined mechanisms of the allergic asthmatic inflammation, led to the hypothesis that release of proinflammatory Th2 mediators and subsequent triggering of the allergic cascade can be prevented when free IgE is almost absent. This knowledge, in turn, spurred the development of omalizumab, a humanized anti-IgE antibody which blocks the interaction of circulating IgE with mast cells and basophils by binding to its FcεR1 epitope. After confirming the original hypothesis by a myriad of both randomized double-blind, placebo-controlled and naturalistic trials as well as real-life surveys, the anti-IgE treatment principle has moved from bench to bedside: Omalizumab is establishing itself in the routine care of allergic asthma patients with severe uncontrolled allergic asthma (i.e. uncontrolled asthma on GINA step 4) as preferred controller option in step 5 and who, previously, had few therapeutic options available. As a result, most patients with the phenotype severe uncontrolled allergic asthma can now be satisfactorily treated. Potential future indications for omalizumab besides chronic spontaneous urticaria worthy of mention could include non-allergic asthma, atopic eczema, Churg-Strauss syndrome [107-109], latex [110] and peanut allergies [111].

Overwhelming data from clinical trials and surveys lasting as long as 3 or more years had strongly indicated that both exacerbations and asthma symptoms can be effectively managed by targeting specific IgE-mediated pathophysiological allergic mechanisms with anti-IgE (omalizumab). Moreover, allergic co-morbidities, i.e. persistent or intermittent rhinitis, which can in turn trigger asthma severity, can also be improved. Co-existent seasonal allergic symptoms in those patients are also successfully targeted. Several other indications, i.e. urticaria, allergic rhinitis with polyps, polyposis nasi and eczema are under investigation.

Omalizumab is a guideline-listed add-on option with high evidence grade to standard guideline-driven asthma therapy for allergic asthma on GINA treatment Step 4 or 5. It is efficacious and safe in improving a range of major outcomes – from clinically significant and severe exacerbations and symptoms to steroid reduction and quality of life.

That said, many challenges remain: The differing international indications and dosing regimens need to be harmonized. There is agreement that the dose and frequency of omalizumab for asthma has to be adjusted according to baseline IgE (IU/ml) and body weight (kg), whereas there are differences between the EU and the USA in terms of dose intervals, maximum dose and also indications. Unlike in Europe, for example, American children younger than 12 years of age may not (yet) be treated with omalizumab.

Unlike asthma, csU should be treated with fixed dose 300mg monthly dose, independent of IgE level and no proof of allergic state before treatment is necessary.

Future perspectives include other challenging questions: What is the minimum effective dose? Does the dose differ for different indications, i.e. asthma vs. not yet approved indications, e.g. non-allergic asthma, nasal polyps, allergic bronchopulmonary aspergillosis, or eczema? Can patients with potentially allergic diseases but without elevated serum IgE (e.g. obviously not allergic asthma, nasal polyps, urticaria) benefit from anti-IgE treatment? When effective in achieving asthma control, can omalizumab be given indefinitely or should it be stopped? Who are non-responders despite the correct indication? How to proceed when there is no response to omalizumab? How to treat patients who are outside the weight and IgE level specifications?

The practical guidelines and dosing tables supplied with omalizumab make it easy for pulmonologists and allergy specialists to integrate IgE blockade with omalizumab into their routine care. With proper management, even severe uncontrolled patients can achieve long-term asthma control while long-term dosing strategies and further indications are being tested.

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Conflict of Interest

Conflict of interest according to the issue of this article: the author received lecture fees and honoraria from Novartis according to omalizumab.

Highlights

- The ATS and ERS published new guidelines defining severe asthma in 2014
- In May 2014, GINA also published a new update of his guideline changing the place of omalizumab: for patients with moderate or severe allergic asthma, that is uncontrolled on step 4 treatment, omalizumab is regarded first line treatment before oral maintenance corticosteroids should be added (treatment step 5).
- IgE blockade is clinically efficacious in managing allergic

asthma, a chronic inflammatory disorder of the airways.

• Narrative review of the literature and report of 14 years of the author's experience with omalizumab in randomized controlled trials, real-life surveys and in clinical routine with the marketed drug.

• The humanized anti-IgE antibody omalizumab is a safe and effective add-on treatment option for patients with inadequately controlled, persistent severe IgE-mediated asthma, recommended in GINA guidelines based on high-grade evidence.

• Important asthma websites for patients:
http://www.asthma.org.uk/
http://www.aafa.org/
http://www.ginasthma.org/
http://asthma.de

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