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Anti-IgE therapy with omalizumab in asthma and allergic rhinitis

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The pharmacology, efficacy, dosage, adverse effects, and economics of anti IgE (omalizumab) are discussed. Omalizumab is the generic name for the human/murine chimeric (recombinant humanized) monoclonal IgG antibody. Anti-IgE prevents IgE from attaching to effector cells, and thereby blunts IgE-mediated inflammatory responses. After subcutaneous administration its absorption is slow, reaching peak concentration in serum after an average of 7–8 days. At recommended doses, serum free IgE levels decrease within 1 hour following the first dose and are maintained between doses. Dose and dosing frequency are adjusted according to body mass and serum total IgE concentration before the start of treatment. Omalizumab administered subcutaneously is an effective treatment for add-on therapy in patients with poorly controlled, moderate-to-severe allergic asthma and allergic rhinitis (adults and adolescents > 12 years). It reduces the requirement for inhaled corticosteroids while protecting against disease exacerbation. Omalizumab is well tolerated, but the safety profile requires long-term assessment in adults as well as in children.

Keywords: asthma, allergic rhinitis, therapy, anti-IgE, omalizumab

INTRODUCTION

Immunoglobulin E (IgE) is fundamental for the development of atopic inflammatory processes and the resulting diseases. Although the role of IgE seems crucial in the defence against parasites (1), this aspect has not been studied to the extent comparable to atopy, or only in as much as it may influence the development of atopic disease (2). Because of the central importance of IgE in asthma and other allergic diseases, researchers have long hypothesized that preventing these IgE-mediated processes should reduce the severity of these disorders. Asthma and allergic rhinitis in particular are clearly related (3), although much remains to be explained. Up to 60–78% of asthmatics have al-

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lergic rhinitis and 38% of patients with allergic rhinitis have coexisting asthma (4). Understanding of asthma and allergic rhinitis has evolved recently the historic perspective of these allergen-induced disorders as distinct and separate entities is being displaced by the current thinking that they are better described as a continuum of inflammation involving one common airway (5). Evidence points to a causal or coincidental relation between these upper and lower airway diseases (6). Despite effective modern therapies for these two allergic disorders, involving primarily topical corticosteroids, the frequent dissapointment with failure to attain treatment goals (7) and their common pathogenetic origin exemplified by IgE has led to the idea of a »united airway disease« or »one-airway disease«, lending itself to a comprehensive (»united«) treatment guideline (8). Rather than following in these footsteps, a monoclonal antibody directed against IgE (omalizumab) has been independently developed, anticipating the invoked unitedness of atopic disease (9). This molecule is a highly specific, highly humanized, non-anaphylactogenic monoclonal antibody that binds to circulating IgE and prevents it from binding to its receptors on effector cells. Data so far indicate that omalizumab brings the circulating IgE to undetectable levels in a dose-dependent fashion. Clinically, it is effective in improving asthma and allergic rhinitis in patients with and without concomitant pharmacotherapy and/or conventional immunotherapy (10), and it may have the potential of treating a wider spectrum of atopic diseases (11) with a very favourable safety profile.

The aim of this article is to review the pharmacology, efficacy, adverse effects and safety of omalizumab, focusing on the treatment of allergic asthma and allergic rhinitis in adults as well as in children.

MONOCLONAL ANTI-IgE-ANTIBODY: OMALIZUMAB

Chemistry and function

Omalizumab (brand name: Xolair®) is the generic name for the human/murine chimeric (recombinant humanized) monoclonal IgG antibody (Fig. 1). Its molecular mass is approximately 150 kDa. The specific antibody-binding site, making < 5% of the total molecule, is of murine origin (variable amino-terminal domains in both heavy and light chains), whereas the remaining IgG molecule is of human derivation – $IgG_1\kappa$ (constant domains in light κ chains and constant domains in heavy γ chains, CH1, CH2 and CH3) (Fig. 1). This confers to the omalizumab two of its most important safety aspects: low--immunogenicity due to an extremely low content of murine components, and non-complement binding properties due to the human part of the molecule. Chemically, it is defined as Immunoglobulin G, anti-(human immunoglobulin E Fc region) (human-mouse monoclonal E25 clone pSVIE26 γ-chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 κ-chain, dimer, or as Immunoglobulin G (human-mouse monoclonal E25 clone pSV1E26 γ-chain anti-human immunoglobulin E Fc region), disulfide with human--mouse monoclonal E25 clone pSVIE126 κ-chain, dimer (12, 13). The binding occurs in the Cε3 domain of the IgE molecule, which is also the binding site for the high affinity IgE receptor. The anti-IgE antibody is needed to block binding of IgE to Fc∈R1 on mast cells and basophils without crosslinking IgE and triggering degranulation of IgE-sensitized cells, *i.e.*, the antibodies need to be non-anaphylactogenic (14). To achieve this, mo-

noclonal antibodies against IgE have been developed that bind IgE at the same site as the high-affinity receptor. Omalizumab-IgE complexes are relatively small, the largest complexes being hexamers containing three molecules each of omalizumab and IgE (15). IgE complexed to anti-IgE is unavailable to bind to receptors on IgE effector cells (Fig. 2). It has been reported to decrease serum IgE levels in a dose-dependent manner, inhibit early allergic reaction (EAR) and late allergic reaction (LAR), and to cause a down-regulation of Fc∈R1 receptors on basophils (16).

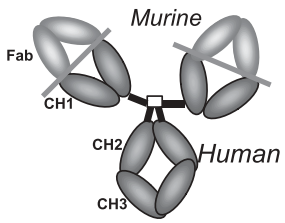

Fig.1. Chimeric antibody made of both mouse and human antibodies.

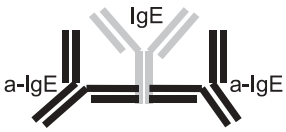

Fig. 2. Anti-IgE binds free IgE.

The IgE-anti-IgE complexes appear to serve as competitive inhibitors of cell-bound IgE (mast cells and other effector cells) (17). The downregulation of CD23 may ultimately shift the cytokine milieu away from a T helper cell type 2 proclivity (18) and interrupt the allergenic cascade at its primary step (the binding of allergen-specific IgE to mast cells). In contrast, other drugs (inhaled corticosteroids, antihistamines, antileukotrienes) act at steps in the cascade following mast cell activation and degranulation (19). It also causes a rapid decrease in dendritic cells surface Fc∈R1 expression and IgE appears to be an important regulator of Fc∈R1 expression by dendritic cells (20). The anti-IgE also removes IgE from the circulation, basophils and mast cells (21, 22).

Pharmacokinetics and pharmacodynamics

Early versions of omalizumab were tested in pilot studies that examined intravenous, subcutaneous and aerosolized administrations. Recently, it culminated in the development of a lyophilized product for subcutaneous administration. After subcutaneous administration, omalizumab is slowly absorbed (over several days) with an average absolute bioavailability of 62%. Its absorption is slow, reaching peak concentration in serum after an average of 7–8 days (23–25). The pharmacokinetics of omalizumab is linear at doses higher than 0.5 mg kg^{-1}. Following multiple doses of omalizumab, areas under

the serum concentration-time curve from day 0 to day 14 at steady state are up to 6-fold of those after the first dose (26). The volume of distribution is 78 ± 32 mL kg^{-1}, approximating the plasma volume, and the half-life is about 26 days, with apparent clearance averaging 2.4 ± 1.1 mL kg^{-1} day^{-1}. Clearance of the omalizumab-IgE complex from the body proceeds like IgG clearance processes, *i.e.*, by liver elimination, which includes degradation in the liver reticuloendothelial system (RES) and endothelial cells and excretion in bile. The omalizumab-IgE complexes have a serum half-life of approximately 20 days (27). The half life of omalizumab-IgE complexes in the blood is about 26–28 days (25, 26).

At recommended doses (Table I), total serum IgE (omalizumab-IgE complex and free IgE, i.e., bound and unbound) concentration increases after the first dose due to the formation of omalizumab-IgE complexes, which have a slower elimination rate compared with free IgE. Sixteen weeks after the first dose, total IgE levels were 5-fold higher than baseline levels. On the other hand, serum free IgE decreased in a dose dependent manner within 1 hour following the first dose and remained at this level between the doses. Finally, as a result of complex formation, the concentration of total IgE in serum is increased, and concentration of free IgE is decreased. In such a manner, total IgE levels do not return to pre-treatment levels for up to 1 year after discontinuation (24, 25).

DOSAGE AND ADMINISTRATION

Suppression of free IgE is deemed to be necessary for optimal efficacy (25). Dose and dosing frequency are adjusted according to body mass and serum total IgE concentration pretreatment (Table I). Corne *et al.* (24) investigated the correlation between the dose of anti-IgE and serum IgE concentration. The intravenous dose of 3 mg of anti-IgE antibody resulted in a decrease of serum free IgE from 495.8 kIU L^{-1} (pretreatment value) to 53.8 kIU L^{-1}, and the administration of 100 mg of anti-IgE antibody caused suppression of total serum IgE from 2317 kIU L^{-1} to 7.3 kIU L^{-1}, respectively. Time of recovery ranged from 1 day (for the 3 mg dose) to 39 days (for the 100 mg dose) (24). Therefore, therapeutic monitoring of free IgE levels during anti-IgE treatment appears to be a desirable tool (24, 28). The monthly dose is calculated according to the next formula (19):

$$0.016 \times \text{body mass (kg)} \times \text{serum total IgE (kIU L}^{-1}) = \text{monthly dose of omalizumab (mg)}$$

A hypothetical 70-kg patient with an IgE concentration of 700 kIU L^{-1} would require $0.016 \times 70 \times 700 = 784$ mg per month, a 50-kg patient with an IgE concentration of 300 kIU L^{-1} would require 240 mg per month, and a 85-kg patient with an IgE concentration of 500 kIU L^{-1} would require 680 mg per month. Owing to the volume of injection, omalizumab doses higher than 300 mg per month must be given in divided doses every 2 weeks. No more than 150 mg is injected at a single site. Some owerweight patients or who have very high IgE concentrations (> 700 kIU L^{-1} for adults and > 1300 kIU L^{-1} for children) or both may not be able to receive omalizumab. In such patients, the calculated dose would be too large to be given in two subcutaneous injections per month. At present, omalizumab cannot be administered to patients requiring more than 750 mg per

month. Repeated determination of serum IgE concentration cannot be used to adjust the dose, as total concentrations (when using standard assays), which measure both the omalizumab-IgE complex and free IgE, are elevated (26).

In view of the risk of anaphylaxis, it is recommended that omalizumab be given in the office of a physician capable of treating anaphylaxis. The patients should be observed for a period of time before leaving the office (19).

Table I. Proposed dose regimen charts from the package insert[a]

Baseline IgE (kIU L^{-1})	Body mass (kg)				
	30–60	> 60–70	> 70–80	> 80–90	> 90–150
≥ 30–100	150	150	150	150	300
> 100–200	300	300	300	300	
> 200–300	300				
> 300–400		ADMINISTRATION EVERY 2 WEEKS			
> 400–500					
> 500–600					
≥ 30–100					
> 100–200		ADMINISTRATION EVERY 4 WEEKS			225
> 200–300		225	225	225	300
> 300–400	225	225	300	300	
> 400–500	300	300	375	375	
> 500–600	300	375		DO NOT	
> 600–700	375			DOSE	

[a] XOLAIR doses (in mg) for subcutaneous administration to adults and adolescents (patients with allergic asthma ≥ 12 years of age) (25).

CLINICAL OUTCOME

Omalizumab is not a first-line therapy in asthmatic patients. FDA approved omalizumab use in June of 2003 for patients satisfying the following criteria (all must be present):

(*i*) total IgE concentration in serum 30–700 kIU L^{-1}: if IgE is < 30 kIU L^{-1}, there is too little substrate for the anti-IgE to bind, if IgE is > 700 kIU L^{-1} (> 1300 kIU L^{-1} in children), the volume of the omalizumab injection needed will be too large;

(*ii*) skin test positive for at least one perennial allergen;

(*iii*) specific IgE concentration positive for at least one perennial allergen (house dust mite, cat and dog);

(*iv*) asthma: moderate to severe persistent asthma;

(*v*) age: ≥ 12 years;

(*vi*) inadequate control despite inhaled corticosteroids.

Omalizumab is used for the management of moderate to severe persistent asthma in adults and adolescents 12 years of age and older. An algorithm of asthma care including omalizumab is presented in Table II (19). Omalizumab should be considered for patients in any of the next categories: whose symptoms are inadequately controlled with inhaled corticosteroids, namely those with persistent and significant symptoms or reversible airflow obstruction as measured by spirometry; those dependent on oral steroids; those on multiple-drug asthma therapy (*e.g.*, inhaled corticosteroids combined with a long-acting beta-agonist, a leukotriene modifier drug or theophylline), those who have had adverse effects from corticosteroids, or are at increased risk of them (19, 29). Omalizumab is recently used in children younger than 12 years (16). It is reported that omalizumab has been also approved for the treatment of allergic rhinitis. Patients with pollenosis have a seasonal increase of both total and specific IgE concentration in serum. This increase would have no impact on omalizumab doses in the majority of patients.

Table II. Omalizumab in an algorithm of asthma care[a]

CONFIRM DIAGNOSIS OF ASTHMA DETERMINE LEVEL OF ASTHMA SEVERITY AND CONTROL			
Mild, intermitent	Mild, persistent	Moderate, persistent	Severe, persistent
Prescribe	Prescribe	Prescribe	Prescribe
As needed, ISAβA	Low-dose ICS plus, as needed, ISAβA, or (not preferred) antileukotriene or theophylline	Low or moderate dose ICS plus LAβA plus, as needed, SAβA, or (not preferred) low or moderate dose ICS plus antileukotriene theophylline	High-dose ICS plus LAβA plus, as needed, ISAβA or (not preferred) high-dose ICS, plus antileukotriene or theophylline
If control is adequate, schedule regular follow-up If control is inadequate, as follows:			
Add low-dose ICS	Add LAβA	Re-assess for asthma triggers Consider referral to an asthma specialist Change to high-dose ICS plus LAβA plus, as needed, SAβA Consider adding theophylline, antileukotriene or omalizumab	Consider adding oral corticosteroid Re-assess for asthma triggers Consider referral to an asthma specialist Change to high-dose ICS plus LAβA plus as needed SAβA Consider adding theophylline, antileukotriene or omalizumab

ICS – inhaled corticosteroid
ISAβA – inhaled short-acting beta-agonist
SAβA – short-acting beta-agonist
LAβA – long-acting beta-agonist
[a] According to ref. 19.

Individual variations, however, can be large and require a dose correction (28). Many asthmatics, morever, have additional sensitisations against seasonal pollen-allergens, and seasonal exposure may increase total and specific IgE levels. Those patients sometimes require additional administration of omalizumab (28).

Results of clinical trials demonstrated that omalizumab administered subcutaneously is an effective treatment for add-on therapy in patients with poorly controlled, moderate-to-severe allergic asthma (23, 30, 31), as well as for patients with allergic rhinitis (32, 33). In most patients, the dosing formula will lead to prescribing enough anti-IgE to bind over 98% of free IgE (34). To achieve effective treatment, patients should be treated with omalizumab for a minimum duration of 12 weeks (35). Omalizumab's ability to form complexes with unbound IgE translates into decreased unbound serum IgE levels and high-affinity IgE receptors on basophils, as well as attenuation of early and late allergic response in patients with allergic diseases. A marked reduction in circulating free IgE levels has been shown to reduce symptoms in those patients (36). Milgrom *et al.* (16) reported that the median concentration of free IgE in serum decreased significantly (95–99%) in the omalizumab treated children aged 6 to 12 years (from 133 to 790 kIU L^{-1} at baseline to 6 to 9 IU L^{-1} during the treatment period).

Studies in asthma

Treatment protocols were conducted in Europe and the United States in moderate to severe allergic asthmatic patients who continued to show symptoms despite treatment with inhaled corticosteroids. At present, the peer-review published double-blind, placebo-controlled studies showed that treatment with anti-IgE allowed a decrease in inhaled corticosteroid and rescue medication use and significantly reduced the incidence and frequency of asthma exacerbations among the patients (37). One of the core studies in moderate to severe allergic asthmatics mean Forced Expiratory Volume in 1st second (FEV1) at baseline 70%) showed, over a 7-month period, a decrease of asthma exacerbation rate for more than 50% during the stable steroid phase (16 weeks) as well as during the phase of inhaled steroids reduction (38). The double-blind placebo-controlled extension of this study by 24 weeks demonstrated a significant improvement in the asthma related quality of life over placebo (39). In a further article, the same authors analyzed long-term effects of omalizumab on the same subjects that were now entered into the double-blind extension trial (40). The asthma control was improved despite significantly lower daily inhaled steroid dosage (253 μg *vs.* 434 μg beclomethasone per day): asthma exacerbation rate was more than halved on omalizumab, concomitant medication use was significantly lower, while the incidence of adverse events was similar in the two groups. A further 12-months double-blind placebo-controlled study of moderate to severe allergic asthma in subjects 12 years and older confirmed the add-on value of omalizumab to the best standard treatment (31). In addition to halved exacerbation rates and significantly reduced rescue medication, this study demonstrated a significant increase in FEV1 of 0.2 L (from average 2.28 to 2.48 L). The SOLAR study was designed to examine the benefit of omalizumab in patients 12 years and older with moderate to severe allergic asthma and concomitant persistent allergic rhinitis over 28 weeks in a randomized double-blind placebo-controlled fashion (41). The drug was well tolerated and produced a decrease in asthma exacerbation rate by a factor of 1.5. Simultaneously, it improved the

asthma and rhinitis related quality of life and the asthma/rhinitis composite symptom score. The baseline treatment of the patients was not changed and was required to be > 400 μg budesonide via Turbuhaler at study entry. Other studies have equally demonstrated that omalizumab allows reduction of inhaled steroid dose (beclomethasone or equivalent 227 μg *vs*. 336 μg per day) while maintaining improved asthma control (30% decrease in exacerbation rate over placebo) (30). As Rambasek *et al*. (19) reported, it is unclear if the clinically meaningful benefit observed in patients on moderate-dose inhaled corticosteroids would also occur in sicker patients on high-dose inhaled corticosteroids plus long-lasting beta-agonists (population to which omalizumab is, at present, most directed). In patients randomized to receive either omalizumab or placebo, Holgate *et al.* (42) reported that patients who were primarily using high doses of inhaled corticosteroids (fluticasone, average dose > 1.3 mg per day) could significantly reduce the inhaled dose (42).

Djukanovic *et al.* (43) investigated the influence of omalizumab on airway inflammation. Outcomes included inflammatory cells in induced sputum and bronchial biopsies, and methacholine responsiveness. Sixteen weeks treatment with omalizumab resulted in a marked reduction of serum IgE. Diminished number of eosinophil granulocytes was associated with a significant reduction in tissue eosinophils, FcepsilonRI+ cells, CD3+, CD4+ and CD8+ T lymphocytes, B lymphocytes, and cells staining for IL-4+ but not with improvement in airway hyper-responsiveness to methacholine. This study showed anti-inflammatory effects of omalizumab. The lack of effect of omalizumab treatment on methacholine responsiveness suggests that IgE or eosinophils may not be causally linked to airway hyper-responsiveness to methacholine in mild to moderate asthma (43).

Studies in seasonal allergic rhinitis

Multiple investigations have shown omalizumab to be an effective agent in IgE-mediated allergic rhinitis (32, 44, 45). The main outcome measures were the increased IgE concentration in serum as well as the self-assessed daily nasal symptom severity score and the frequency of rescue antihistamine use. The nasal symptom scores were significantly lower with the 300-mg dose of omalizumab (44). Nayak *et al.* (46) found omalizumab to improve the rhinitis-specific quality of life. Omalizumab appeared to be a well tolerated agent (28, 29), even in retreatment during a second ragweed pollen season (46), although the safety profile requires a longer-term assessment (41). It was clearly shown that a 16-week omalizumab treatment in patients with allergic rhinitis almost fully attenuates nasal symptoms on allergen challenge, stops albumin exudation and significantly reduces tumor necrosis factor alpha (TNF-alpha) in nasal lavage fluid (44). Interestingly, the histamine content of the nasal lavage fluid remained unaffected. Significant blunting of clinical nasal symptoms can be expected within 2 weeks of the first dose of omalizumab (47). Elimination of 96% of free IgE occurs within 3 days, and downregulation of 73% of high-affinity-epsilon-receptor FcERI on basophils within 14 days.

Studies in children

FDA has approved omalizumab use only for patients aged 12 years or older, although the core study was conducted on children 6–12 years of age (16). This study has shown, similarly to the studies in adults, that regular omalizumab therapy allows signifi-

cant inhaled steroid dose reduction while maintaining protection against exacerbation. Further investigation of the subjects in the aforementioned study has established a significant improvement in the asthma related quality of life (48). Another study has confirmed that these clinical effects are accompanied by improvement in the markers of inflammation (49). The results showed that treatment with omalizumab may inhibit airway inflammation during steroid reduction in children with allergic asthma measured by a significant decrease of exhaled nitric oxide from pretreatment 41 ppb to 18 ppb in week 52 of treatment, despite concurrent decrease in the dose of inhaled steroids.

Berger *et al.* (50) evaluated the long-term (52-week) safety profile. They found that the safety and tolerability of omalizumab in children was largely comparable to placebo (the most common adverse event was upper respiratory infection: 47% in omalizumab *vs.* 43% in the placebo group, not siginficant). Patients in the omalizumab group exhibited urticaria in 4.9% of patients, which was generally well controlled with antihistamine treatment, and resulted in withdrawal from treatment in only 1 out of 11 patients.

It has also been shown that children with seasonal allergic rhinits can benefit from omalizumab in terms of significant reduction of symptoms (48% over specific immunotherapy alone), steroid and rescue medication use when used in combination with specific immunotherapy (51). Reduction in *ex vivo* leukotriene release from peripheral leukocyte on specific allergen challenge in the treated subjects seemed to parallel the clinical effects (52). However, the quantification of endogenous leukotrienes in urine produced equivocal results (53).

According to the Omalizumab Rhinitis Study Group, anti-IgE monotherapy significantly diminished rescue medication use and number of symptomatic days in children aged 6–17 years with seasonal allergic rhinitis. The combination of anti-IgE and specific immunotherapy showed superior efficacy to each treatment alone during the first year of observation (32). The combination of specific ummunotherapy (SIT) and anti-IgE in children with seasonal allergic rhinoconjunctivitis is associated with prevention of nasal specific immunotherapy (ECP) increase and decreased tryptase levels in nasal secretions (33). The results were similar to those seen for inhaled corticosteroids alone, meaning that omalizumab has significant antiinflammatory effects (49). Omalizumab reduces leukotriene (LT) release of peripheral leukocytes stimulated *in vitro* with allergen in children with allergic rhinitis undergoing allergen immunotherapy, but urinary LTE4 concentrations are not helpful in monitoring patients treated with anti-IgE and SIT (53).

TOLERABILITY AND SAFETY

The limited clinical data currently available suggest that anti-IgE treatment with omalizumab did not cause any of the complications that might, in theory, be expected to result from a reduction in circulating free IgE, such as adverse effects upon the immune system or other body systems (54). According to some reviewers, the results of clinical trials demonstrated that omalizumab administered subcutaneously is a safe and effective treatment for moderate to severe allergic asthma, since it generally has a mild adverse effect profile (23, 24, 30). In patients with seasonal allergic rhinitis there are no severe or serious adverse events related to omalizumab treatment. Retreatment during a

second pollen season with omalizumab, 300 mg every 3 or 4 weeks, was not associated with any significant immunologic reactions (46). There are many documented clinical adverse events as well as laboratory arguments that can be classified in several groups: most frequent (injection-site reactions, viral infections), severe (malignancy), rare (rash) and laboratory (decreased hemoglobin) (Table III) (41, 46, 55, 56). Besides, the safety profile requires long term assessment (28, 29).

The most frequent adverse events in asthma patients receiving omalizumab include injection-site reactions (45%), viral infection (23%), upper respiratory tract infection (20%), sinusitis (16%), pharyngitis (11%), or headache (15%). Injection-site reactions include redness, warmth, burning, stinging, itching, hive formation, pain induration, and inflammation. The local reaction, that usually occurs within one hour of the injection, lasts up to 8 days (24). Randomized placebo-controlled studies indicate that omalizumab displays a very favourable safety profile when used for treatment of asthma in adults (31, 41) as well as in children (16). Almost 17% patients receiving anti-IgE experienced adverse effects (compared to 12% in placebo group). Serious adverse events were recorded in 1.4% of the omalizumab group (1.5% in placebo group) (25, 26). The proportion of subjects experiencing events such as headache, pharyngitis, sinusitis, influenza, upper respiratory tract infection and bronchitis did not differ significantly from the placebo group. The principal adverse events judged to be drug related were injection site reactions (7–8% *vs.* 4–5%) and urticaria (1–2% *vs.* 0–1%).

No patient developed anti-omalizumab antibodies and there was no evidence of immune complex disease (31). According to Berger *et al.* (50), there is no evidence that

Table III. Adverse events of omalizumab administration[a]

Most frequent adverse events	Injection-site reactions
	Viral infection
	Upper respiratory tract infection
	Sinusitis
	Pharyngitis
	Headache
Rare adverse events	Rash
	Disgestive system events
	Bleeding-related events
	Female genitourinary events
	Events among the geriatric population
Severe events	Malignancy
	Anaphylaxis
Clinical laboratory arguments	Decreased hemoglobin
	Thrombocytopenia
	Mild leukocyte decrease

[a] According to refs. 25, 26, 28, 29.

new or more serious adverse events occur with long-term omalizumab treatment in children. No anti-omalizumab antibodies were detected in any of the children (50).

The most noteworthy serious adverse events are malignancy and anaphylaxis. Subcutaneous injections with a monoclonal anti-immunoglobulin E antibody for ragweed or birch allergic rhinitis produced few anaphylactic reactions but when reactions did occur, they appearred 90–120 minutes after the injection (57).

It is not known whether IgE plays a surveillance role in cancer prevention, though there is evidence of its role in protection from a variety of environmental carcinogens and infectious diseases (58). Malignancies appear to be observed less frequently in the closest relatives of patients suffering from hay fever with the documented hereditary liability to atopy than in the relatives of control groups (59). It was recently documented that the history of asthma and hay fever were associated with a trend toward a reduced risk of colorectal cancer and increased risk of leukemia, but these results were not statistically significant. No association was found between breast and lung cancers and allergic disorders or atopy (59).

If IgE is blocked (with anti-IgE antibody), there is a theoretical question of whether there is an associated increase in cancer incidence. According to Vignola *et al.* (41), serious adverse events were observed in 1.4% of omalizumab-treated patients and 1.5% of placebo-treated patients. In the studies that were submitted to obtain FDA approval, the incidence of new or recurrent cancer was 0.5% with omalizumab and 0.2% with placebo. The types of malignancies observed included breast, melanoma, non-melanoma skin, prostate, and parotid. Most patients were observed for less than a year (25). Consequently, a shorter period than that in which oncogenesis can be usually observed, and because the tumors involved various organs, it is reasonable to doubt that these cancers were caused by omalizumab. It is unknown if longer exposure or use in patients with higher risk factors for malignancy increases the risk of developing cancer. On the other hand, there are no published data that provide a direct pathophysiological link between anti-IgE therapy and cancer development or progression, but the potential for alterations in the function of IgE-mediated effector cells (mast cells, eosinophil granulocytes) must be considered. Alteration of these functions by anti-IgE therapy may, theoretically, affect the resistance to cancer.

Influence on laboratory findings

In general, clinical laboratory data are most remarkable for the decreased hemoglobin concentration and mild platelet counts in some patients. In animal studies (with high doses of omalizumab), serum omalizumab concentrations correlate most closely with platelet decrease. The doses used in clinical studies were considerably lower than those associated with thrombocytopenia in animals. The observed decreased leukocyte number was low and clinically inconsequential. In general, these events were associated with viral-type illnesses or were isolated time point findings. No subject developed persistent neutropenia and no subject experienced a decrease in white blood cells count below 2.3×10^9 per litre.

A Cochrane meta-analysis of eight trials involving 2037 mild to severe asthmatic patients pointed to the conclusion that omalizumab was well tolerated, but the safety profile required longer-term assessment in adults as well in children (55, 56)

COST ANALYSIS

Biological agents are expensive to produce. Omalizumab is far more expensive than other asthma medications. The average wholescale price of omalizumab will be $433 per vial, putting the annual cost per patient at roughly $10,000 to $12,000 (60, 61). Children tend to need higher doses as they usually have higher IgE levels. A calculation of the cost of co-seasonal application of an average 0.016 mg per kg per IU IgE per month in children 6–17 years of age with hay fever yielded a mean of 1253 € per patient per month which, compared to specific immunotherapy (425 € in the first year of treatment) was more expensive, but also significantly more effective (32). A retrospective economic analysis was performed to determine the cost-effectiveness of omalizumab using 52-week data from 2 randomized controlled clinical trials in adults and adolescents with moderate-to-severe allergic asthma. Only direct costs were considered. Omalizumab administration could be cost-saving if given to nonsmoking patients who are hospitalized 5 or more times or 20 days or longer per year despite maximal asthma therapy with older drugs (61). The dosage of omalizumab depends on the patient's body mass and serum IgE concentration, meaning that a small patient with slightly elevated IgE might require one vial per month ($5,196 per year); a larger patient with an IgE concentration of 600 kIU L^{-1} could require as many as five vials per month ($25,980 per year) (19) The high cost associated with omalizumab treatment may be prohibitive for some patients, thereby limiting its utility (23). Omalizumab could be cost-effective for patients with seasonal asthma, since it would not need to be used year-round (19).

FUTURE RESEARCH

Despite many studies addressing the role of anti-IgE antibody in patients with allergic diseases of airways, a number of questions remain:

(*i*) Is it beneficial in less than severe or moderate asthma?

(*ii*) Can it prevent the onset of asthma in patients with allergic rhinitis?

(*iii*) Is it going to have a role in childhood asthma?

(*iv*) Can it prevent airway remodeling?

(*v*) Does it facilitate specific immunotherapy?

(*vi*) Can it be used in food allergy?

(*vii*) What effect does it have on atopic dermatitis?

(*viii*) Is it effective in nonatopic asthma?

Also, it remains to be determined whether omalizumab might be beneficial to patients with intrinsic asthma, who may also overexpress Fc∈R1receptors within their bronchial mucosa (62).

Symbols. – CD – Cluster of Differentiation; EAR – Early Allergic Reaction; ECP – Eosinophil Cationic Protein; Fc – Fc-fragments; Fc∈R1 – High-affinity-Epsilon-Receptor; FEV1 – Forced Expiratory Volume in 1st second; ICS – Inhaled Corticosteroid; IgE – Immunoglobulin E; IgG – Immunoglobulin G; IL – Interleukin; ISAβA – Inhaled Short-Acting Beta-Agonist; LAβA – Long-Acting Beta-Agonist; LAR – Late Allergic Reaction; LT – Leukotriene; RES – Reticuloendothelial System; SAβA – Short-

-Acting Beta-Agonist; SIT – Specific Immunotherapy; SOLAR-study – Study on Occupational Allergy Risks; TNF-alpha – Tumor Necrosis Factor Alpha

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S A Ž E T A K

Anti-IgE terapija astme i alergijskog rinitisa omalizumabom

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Opisani su farmakologija, djelotvornost, doziranje, nuspojave i ekonomičnost primjene anti IgE antitijela – omalizumab. Omalizumab je generičko ime za ljudsko/mišje kimerično (rekombinantno humanizirano) monoklonalno IgG antitijelo. Anti-IgE sprječava vezanje IgE na efektorske stanice i sprječava upalni odgovor posredovan s IgE. Nakon subkutane primjene sporo se apsorbira te dostiže vršnu koncentraciju u serumu nakon 7 do 8 dana. Uz preporučene doze koncentracija slobodnoga IgE u serumu smanjuje se unutar jednoga sata. Doziranje se podešava prema tjelesnoj masi i koncentraciji IgE-a u serumu. Omalizumab je djelotvoran kao dopunska terapija u pacijenata (starijih od 12 godina) sa slabo kontroliranom umjerenom do teškom alergijskom astmom odnosno s alergijskim rinitisom. Smanjuje potrebu za inhalacijskim kortikosteroidima te pogoršanje astme. Dobro se podnosi, ali sigurnost primjene, kako u odraslih tako i u djece, treba još ispitati.

Ključne riječi: astma, alergijski rinitis, terapija, anti-IgE, omalizumab

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