

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/23656884>

Omalizumab: Not Only For Asthma

Article in *Recent Patents on Inflammation & Allergy Drug Discovery* · February 2008

DOI: 10.2174/187221308786241910 · Source: PubMed

CITATIONS

7

READS

122

1 author:



[Moshe Ben-Shoshan](#)

McGill University

183 PUBLICATIONS **1,953** CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



SPAACE [View project](#)



the LACTAAM study (b-lactam and other antibiotic allergies in children) [View project](#)

Omalizumab: Not Only For Asthma

Moshe Ben-Shoshan*

Division of Pediatric Allergy and Clinical Immunology, McGill University Health Center, 418 Claremont app 57 Montreal, Qc, Canada

Received: August 16, 2008; Accepted: September 1, 2008; Revised: September 5, 2008

Abstract: Omalizumab is a recombinant humanized monoclonal antibody. Use of omalizumab is reported to benefit significantly patients with inadequately controlled moderate-to-severe persistent allergic asthma that is not controlled with high-dose inhaled corticosteroids.

However, recent studies suggest that omalizumab might play an important role in the treatment of other potentially IgE mediated disease processes including: urticaria and angioedema, atopic dermatitis, allergic rhinitis, nasal polyposis and severe ocular allergies. Furthermore, addition of omalizumab to immunotherapy protocols is reported to be highly advantageous. Although omalizumab is generally well tolerated, reports on potential anaphylactic reactions as well as an association with Churg-Strauss syndrome necessitate close monitoring. The data reviewed are discussed with the aim of underlining unmet needs and making recommendations for future studies on omalizumab use. This might better guide future clinical practice regarding omalizumab treatment. This review article also discussed some patent related to the field.

Keywords: Omalizumab, asthma, angioedema, urticaria, polyposis, ocular allergy, immunotherapy.

INTRODUCTION

Hypersensitivity reactions mediated by immunoglobulin E (IgE) are associated with several allergic disorders including: asthma, rhinitis, ocular allergies and urticaria [1,2]. Given the central role of IgE in these reactions, a drug that neutralizes IgE might be highly beneficial in patients presenting with allergic disorders.

The medical literature reports increased use of omalizumab (Xolair, Genetech), an IgE neutralizing drug, for various allergic disorders. This paper briefly reviews the development, clinical use and possible drawbacks of omalizumab.

IgE and its Role in Allergic Reactions

IgE molecule heavy chain consists of CH2, CH3 and CH4 domains Fig. (1). IgE concentration in the serum is very low, 1-400ng/ml in non atopics [3-5] and its half life is 2.5 days [6]. IgE levels in the population and even in the same individual at different time points may differ due to genetic variability and environmental factors such as infections [6].

Switching to IgE production and secretion is induced in the presence of cytokines, mainly Interleukin-4 (IL4) and IL13. Binding of these cytokines to their respective receptors induces primarily phosphorylation of Signal Transducer and Activator of Transcription 6 (STAT6). STAT6 dimers reach the nucleus, bind to the epsilon switch promoter and induce epsilon Germ Line (GL) transcription. This effect is enhanced synergistically by nuclear factor-kappa B (NFkB) as well as by the activator protein 1 (AP-1) [6-9]. Furthermore STAT6 and NFkB increase transcription of Activation Induced Deaminase (AID) that has a central role in class

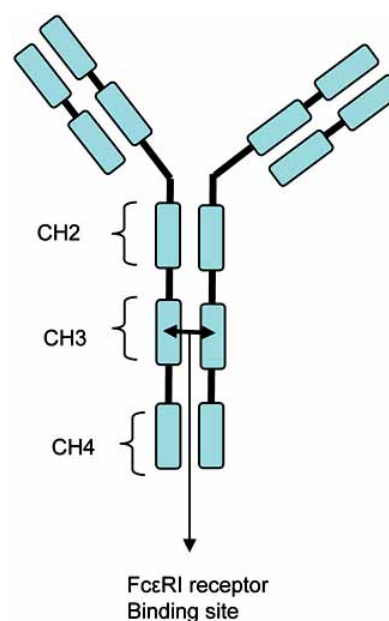


Fig. (1). IgE and FcεRI receptor binding site.

switch. The negative regulators of this process include inhibitor of differentiation-2 (Id2) and B-cell lymphoma 6 protein (BCL6) [10-12].

IgE Receptors

There are 2 types of IgE receptors. Mast cells and basophiles express FcεRI Fig. (2). This receptor consists of 4 subunits. The α subunit binds the CH3 region in the IgE molecule; the β subunit confers stability and amplifies the signal generated by the 2 γ subunits. The $\alpha\gamma_2$ forms are expressed by monocytes, eosinophiles, platelets Langerhans

*Address correspondence to this author at the McGill University Health Center, Montreal, Qc, Canada; Tel: 514-484-2401; Fax: 514-412-4390; E-mail: daliamoshebs@gmail.com

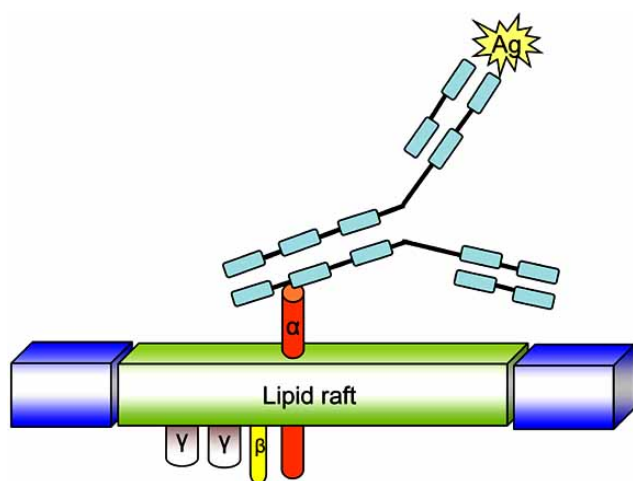


Fig. (2). FcεRI receptor binding IgE

and dendritic cells [13-16] Allergen induced IgE FcεRI cross linkage leads to activation of mast cell or basophile and release of their mediators. In general, serum levels of IgE regulate Fc epsilonRI expression [17].

The second type of IgE receptor, FcεRII also known as CD23, is the low affinity receptor. It belongs to the lectin family of receptors [18] and is expressed by numerous inflammatory cells such as B cells, macrophages and platelets as well as on structural cells such as airway smooth muscle cells [19,20]. It is suggested that this receptor is also involved in allergic diseases through IgE synthesis regulation, enhanced histamine release from basophiles, antigen (Ag)-IgE presentation to T helper 2 (Th2) cells and production of proinflammatory cytokines by macrophages [17,21, 22].

The binding site for both high and low affinity receptor resides in the CH3 domain of IgE [23] and both are up regulated as IgE levels increase [18].

Cascade of Receptor Activation

Cross linking of the IgE receptor stabilizes receptor localization to lipid domains in the plasma membrane known as lipid rafts [24, 25] Fig. (3). In these domains, the active form of the Src family kinase Lyn is protected from dephosphorylation [26] and thus it can phosphorylate and activate the γ subunit of the IgE receptor as well as another src kinase known as Syk [27,28]. Active Syk phosphorylates many substrates including Bruton's tyrosine kinase(BTK), Linker for Activation of T cells(LAT) and through GRB2-associated binding protein 2 (GAB2) activates also phosphatidylinositol 3-kinase(PI3K). PI3K catalyses the synthesis of phosphatidylinositol-3,4,5-triphosphate (PtdIns P3) and phosphatidylinositol-3,4- biphosphate. PtdInsP3 anchors Phospholipase C (PLC) through LAT as well as activated BTK. Thus activated BTK phosphorylates PLC. Active PLC will generate diacylglycerol (DAG) and inositol-1,4,5-triphosphate(InsP3) that serve as second messengers [29].

Syk also phosphorylates SHC adapter protein. Phosphorylated SHC proteins may couple to the Ras signaling

pathway through the formation of a Shc-Grb2-Sos complex [30]. The GTP-bound Ras protein binds to the Raf kinase and initiates a protein kinase cascade that leads to MAP kinase activation. First it phosphorylates a MAP kinase kinase such as Raf. Raf phosphorylates and activates Mek, a MAP kinase kinase. Activated Mek phosphorylates and activates MAP kinase, such as extracellular signal-regulated kinase (ERK). Subsequently, the activated ERK translocates into the nucleus where many of the physiological targets of the MAP kinase signal transduction pathway are located. These substrates include transcription factors that are regulated by MAP kinase phosphorylation. These include Elk-1 that activates phospholipase A (PLA) and c-Fos [31].

VAV is a proto-oncogene protein also activated by Syk. Vav is a guanine nucleotide exchange factor (GEF). The activation of Rac1 by Vav can lead to the activation of c-Jun N terminal (JNK)/stress-activated protein kinase [15, 32] Fig. (3). The end products of RAS and VAV activation, Fos and Jun bind and generate the activator protein 1 (AP-1), a transcriptional regulator [15,33] Fig. (3). The end result of these pathways, induced by IgE binding, is the degranulation of mast cells and basophiles, and generation of lipid mediators and cytokines initiating the allergic process.

Mast cell products induce an immediate allergic reaction within minutes after exposure to allergen. Preformed and newly generated mast cell products include histamine, proteases and arachidonic acid metabolites [15, 33, 34]. Mast cells are also involved in late phase reactions peaking 6-12 hours after allergen exposure and in chronic allergic inflammation, as they were shown to enhance airway eosinophil infiltration [35] and proliferation of cells in airway epithelium [36, 37].

Generation of Omalizumab and Mechanisms of Action

Human IgE administered to mice results in the proliferation of a B cell clone secreting IgG directed against IgE. The B cells are harvested and fused with myeloma cells, thus generating immortalized "hybridoma" cells that secrete an IgG anti-IgE [38]. A single "hybridoma" cell line is used to generate large quantities of monoclonal Ab. Most murine elements are then removed from the antibody in order to prevent undesirable reactions in humans and the light chains of this IgG are incorporated into a human IgG1, to create a 95% humanized Ab [39].

Given that omalizumab binds to the CH3 domain of IgE, IgE is unable to bind its receptors. However, this holds true only for soluble IgE, as IgE bound to its receptor is inaccessible to omalizumab [40, 41]. Omalizumab forms small biologically inert complexes with IgE [19].

Anti allergenic effects of omalizumab are exemplified by *in vitro* as well as by *in vivo* studies. It is reported that omalizumab prevents IgE binding to mast cells, muscle contraction and histamine release after exposure of lung tissue to ragweed [41] or dust mite allergen, Dermatophagoides pteronyssinus [42]. Reports of reduced number of IgE receptors on effector cells associated with omalizumab treatment [43, 44] are in line with the fact that IgE receptors density on effector cells correlates with free IgE levels [45]. Others report that increased omalizumab to IgE ratio at

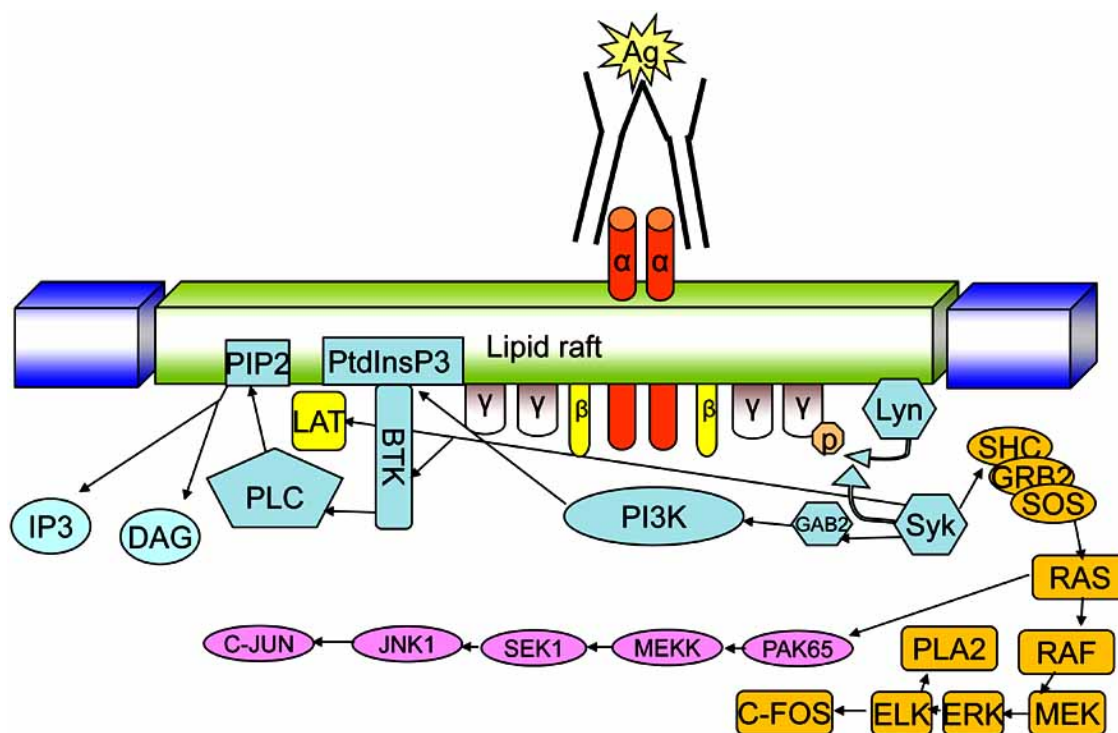


Fig. (3). Cascade of FcεRI activation.

baseline prevented IgE induced receptor up-regulation by 50%, whereas adding omalizumab to mast cells already with IgE-enhanced Fc epsilonRI levels reduced Fc epsilonRI levels to baseline [46]. It is also suggested that by displacement of free autoantibodies or other serum proteins binding to a target tissues, omalizumab may affect disease processes not mediated through IgE [47].

Human studies support the beneficial effects of omalizumab and exemplify a decrease in basophil histamine release during omalizumab therapy in allergic asthmatics [48].

Clinical Uses

Initially omalizumab use was restricted mainly to severe asthmatics.

However, recent reports suggest that omalizumab may play a role in the treatment of other allergic disorders as well as in immunotherapy. Omalizumab dosage may range according to different authors between 0.016-0.50mg/kg and dosage interval is 2-4 weeks Table 1.

Asthma

Atopic asthma is characterized by IgE dependent, positive skin-prick test to a specific set of allergens. Among asthmatics, 10-33% exhibits normal IgE levels and no skin reactivity to specific allergens [49]. Both asthma groups present with Th2 inflammatory response [50], increased numbers of Fc(epsilon)RI-bearing cells in bronchial mucosa [51] and local production of IgE in the bronchial mucosa [52]. Thus, IgE is thought to play a major role in the pathogenesis of asthma in atopic as well as in non-atopic asthmatics [18].

Approximately, 20% of asthmatic patients have severe asthma, of which 20% is inadequately controlled. Patients with inadequately controlled severe persistent asthma are at a particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life. Asthma management focuses on a stepwise approach tailored to disease severity. In addition to needing high-dose inhaled corticosteroids (ICS) and long-acting beta(2)-agonists (LABAs), patients with severe persistent asthma often require additional controller medications, such as anti-leukotrienes, oral LABAs, oral corticosteroids and/or anti-IgE therapy (omalizumab) [53].

Omalizumab is especially beneficial in a subset of patients with very severe asthma and local pulmonary steroid resistance [54]. Omalizumab treatment ameliorates both the early and late asthmatic response [55, 56]. In a retrospective pooled analysis on the effect of omalizumab on asthma in patients (≥ 12 years) with moderate-to-severe persistent IgE-mediated allergic asthma, it was found that omalizumab therapy reduced the need for systemic corticosteroid bursts by 43% [57] and improved effectiveness of asthma treatment [58]. According to the National Heart Lung and blood institute expert panel report 3 omalizumab treatment should be considered as adjunctive therapy in step 5 or 6 care for patients 12 years and older who have proven sensitivity to aeroallergens (but total serum IgE not exceeding 700IU/ml) and severe persistent asthma inadequately controlled with the combination of high dose inhaled steroids and LABAs [59]. Given the role of IgE in the pathogenesis of non-atopic asthma, omalizumab treatment might possibly be advantageous in severe steroid resistant non-atopic asthmatics as well.

Table 1. Off-Label Uses of Omalizumab

Disease	Study (reference number)	Patients characteristics	Number of patients in the study	Dose and duration	Results
ABPA	61	12 yo with Cystic fibrosis and asthma	1	1 dose.	A dramatic and rapid improvement of respiratory symptoms and lung function
Rhinitis and ocular allergy	67	PT 20-64 yo with moderate-to-severe allergic rhinitis +/- ocular allergy induced by Japanese cedar pollens	308	12 weeks with omalizumab 150, 225,300 or 375 mg SC every 2 or 4 wks based on weight and IgE levels (minimum dose of 0.016 mg/kg/IgE [IU/mL]). Initial dose administered at least 1 month before expected pollen period	Significantly lower mean daily nasal and ocular severity scores compared to the controls
Rhinitis	69	Pt 12-75 yo with at least a 2-year history of moderate to severe ragweed-induced seasonal allergic rhinitis	536	50 mg (n = 137), 150 mg (n = 134), or 300 mg (n = 129), or placebo (n = 136) SC just prior to ragweed season and repeated during the pollen season every 3 wks in patients with baseline IgE levels of 151 to 700 IU/mL (4 total treatments) and every 4 wks when baseline levels were 30 to 150 IU/ml	Nasal symptom severity scores were significantly lower in patients who received 300 mg of omalizumab than in those who received placebo
Rhinitis	70	68 yo man with chronic rhinosinusitis, nasal polyposis, persistent asthma and aspirin intolerance	1	225 mg SC every 2 wks	Improvement in asthma symptoms, chronic forehead and paranasal pressure within 2 months, and resolution of nasal mucosa and polypoid swelling within 4 months
Polyposis	71	Pt 31-69 yo with atopic asthma and nasal polyposis undergoing endoscopic surgery	8: 4 treated, age range:31-69 years & 4 controls	150-375 mg every 2-4 wks (according to pt weight & IgE levels)	Significantly improved nasal polyp scores in the anti-IgE group
Urticaria	74	27 yo man,32-yo woman and 48 yo woman with Intractable urticaria	3	300 mg every 2 wks for pt 1 and 375 mg every 2 wks for pt 2 & 3	Clearing of urticaria within 6 wks for pt 1and within 1 wk for pt 2 & 3
Cholinergic uerticaria	76	25 yo man	1	300 mg SC every 2 wks	Decreased symptoms within 3 wks and complete disappearance of symptoms at week 11 of treatment
Cold induced urticaria	77	12 yo girl with severe chronic cold urticaria and asthma resistant to AH treatment	1	375 mg SC every 2 wks	Complete disappearance of symptoms induced by cold and skin sensitivity to ice cube test after 5 months of treatment
Angioedema	80	65 yo man with asthma & sarcoidosis. 63 yo man with COPD 50 yo man with asthma and severe recurrent laryngeal edema resulting in tracheostomy	3	Pt 1: 300 mg SC every 3 wks Pt 2: 375 mg SC every 2 wks Pt 3: 300 mg SC every 4 wks	Pt 1 & 2 were free of angioedema since omalizumab was begun. Pt 3 had had only 1 minor episode during the year after treatment initiated

(Table 1) Contd....

Disease	Study (reference number)	Patients characteristics	Number of patients in the study	Dose and duration	Results
Atopic Dermatitis	87	Recalcitrant Atopic dermatitis	3	Pt 1: 300 mg SC for the first 2 visits and 450 mg for visits 3-12 (2 weeks intervals) Pt 2: 150 mg increased to 450mg Pt 3: 150 mg initially alternating with 300 mg subsequently	Improvement in signs and symptoms of eczema
Food allergy	92	History of immediate hypersensitivity to peanut Randomized DP	84	250 mg, 300 mg or 250 mg TNX-901 SC every 4 wks, sum of 4 doses	450 mg TNX-901 significantly increased thresh hold to peanut challenge (from 178 mg to 2805 mg peanut)
Occupational allergies	96	Health care workers with symptoms of latex allergy for at least 1 year, +SPT & specific IgE of at least 2	18	150 mg to 750 mg/mo depending on body weight and total serum IgE level at base line	Improvement in conjunctival challenge scores. After 32 wks of treatment there was also decrease in skin reaction
Mastocytosis	101	45 yo man with mastocytosis , anaphylactic reaction to bee sting and multiple reactions during venom IT	1	300 mg (twice the dose according to his weight and IgE levels) SC 1 week prior to IT shot and with progressively shorter subsequent intervals (till 1 hour)	Patient tolerated the single 100 mcg maintenance dose without adverse effects
Matocytosis	102	56 yo woman with cutaneous mastocytosis and Ménière's disease	1	150 mg SC every 2 wkss for the first 4 shots and then monthly	After first 4 shots symptoms improved Significantly: no new wheals or pruritus
Ménière's disease	102	56 yo woman with cutaneous mastocytosis and Ménière's disease	1	150mg SC every 2 wks for the first 4 shots and then monthly	Free of debilitating vertigo and nausea
IT	103	SAR moderate-severe and sensitization to birch and grass pollen	221	After IT titration (12 wks) omalizumab was added at 2-4 weeks intervals at a minimum dose of 0.016mg/kg/IU/ml of total IgE	Reduced symptom load, severity rescue medications by nearly 50% over IT alone
EGID	103	Pt 12-76 yo with eosinophilc gastroenteritis	9	375mg every 2 weeks for 16 wks (1 subject received 85mg per dose)	Decreased symptoms score, decreased absolute eosinophil counts
IT	104	SAR sensitization to birch and grass pollen	225	0.016mg/kg/IU/ml of total IgE every 4 weeks contra lateral to IT injections	Significant decrease in symptom severity and use of rescue medications
IT	107	Adult patients with ragweed allergic rhinitis, parallel-group DP	159 enrolled (123 completed)	9 weeks of omalizumab (0.016 mg/kg/IgE [IU/mL]/mo) followed by 1-day rush (maximal dose 1.2-4.0 mug Amb a 1) IT then 12 weeks of omalizumab +IT	Decrease in risk of anaphylaxis caused by RIT (odds ratio, 0.17), significant improvement in severity scores
IT	109	15 yo. Ultra RIT stopped due to anaphylactic symptoms	1	1 dose of 300 mg SC 2 wks prior to IT	No severe side effects

ABPA, Allergic bronchopulmonary aspergillosis; Yo, Year-old; SC, Subcutaneously; Pt, Patients; Wks, Weeks; SPT, skin prick test; DP, Double-blind placebo; SAR, seasonal allergic rhinitis; AH-Antihistamines; COPD, chronic obstructive pulmonary disease; EGID, Eosinophil-associated gastrointestinal disorders; IT; immunotherapy; RIT, Rush immunotherapy

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a disease resulting from a hypersensitivity response to *Aspergillus fumigatus*. It is characterized clinically by wheezing, pulmonary infiltrates, bronchiectasis, and fibrosis that affect patients with asthma and cystic fibrosis [60]. Dramatic and rapid improvement of respiratory symptoms and lung function after a single dose of anti-IgE antibody (omalizumab) in a 12-year-old girl with cystic fibrosis and ABPA is described [61].

Allergic Rhinitis

Allergic rhinitis, an IgE-mediated disease, is the most common chronic childhood condition and is characterized by nasal sneezing, rhinorrhea, palate and eye itchiness, and congestion [62]. Several allergens are associated with allergic rhinitis mainly: house dust mite, grass pollen, and cat [63]. Allergic rhinitis and asthma are inflammatory conditions of the airways that often occur concomitantly and it is suggested that mucosal inflammatory processes that involve the upper airway generally occur in conjunction with lower airway diseases [64]. Furthermore, treating allergic rhinitis is increasingly recognized to contribute to better asthma control [65, 66].

Blocking the effects of IgE by omalizumab, has been shown to be a useful adjunct in the treatment of allergic rhinitis. Omalizumab is more effective than suplastat tosylate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis [67-70]. However, cost and recent warnings of potential risks associated with omalizumab; do not favour its use as a first line treatment in patients with allergic rhinitis.

Nasal Polyposis

Although the etiology of nasal polyposis remains unknown, emerging evidence showing elevated local IgE levels and eosinophilic infiltration suggests an allergic etiology. It was shown that addition of anti-IgE therapy in the postpolypectomy management of atopic asthmatic individuals may reduce the severity of polyposis recurrence [71].

Urticaria

Chronic urticaria is defined when wheals arise spontaneously for a period lasting more than 6 weeks. Physical urticarias are also chronic conditions but are triggered by specific physical factors [72]. A subset of chronic idiopathic urticaria has an autoimmune basis and is caused by circulating autoantibodies against the high affinity IgE receptor (FcεR1) and less commonly against IgE [73].

Hence, not surprisingly, the medical literature reports successful treatment of such patients with omalizumab [74, 75]. There are also reports of successful treatment of cholinergic urticaria and cold urticaria with anti-immunoglobulin E therapy [76, 77].

Angioedema

Angioedema is a self-limited nonpitting edema generally affecting the deeper layers of the skin and mucous membranes. The most frequent syndrome of angioedema is

idiopathic recurrent (38% of patients). Less common angioedema syndromes include: allergic or IgE mediated, hereditary (e.g. C1 esterase inhibitor deficiency), acquired (from acquired C1 esterase inhibitor deficiency) and angioedema associated with angiotensin-converting enzyme inhibitors [78]. It is suggested that angioedema is the end result of 2 possible mechanisms: the mast cell pathway in which preformed mediators, such as histamine, rapidly formed mediators, leukotrienes and prostaglandins, are released from mast cells through IgE or direct activation. This is most common in children and usually associated with food, medications, and infections. The second pathway is the kinin pathway, associated with hereditary forms or with the use of angiotensin-converting enzymes, which results in the formation of bradykinin [79]. The medical literature describes a successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab [80].

Atopic Dermatitis

It is suggested that skin barrier abnormality is crucial in the pathogenesis of atopic dermatitis and that it may result in T helper (Th) cell types 1 and 2 cell dysregulation, IgE production, mast cell hyperactivity, and dendritic cell signalling. The end result will be a chronic inflammatory pruritic dermatosis [81]. Allergens, including food allergens and inhalants such as house dust mite and cat allergens play a major role in atopic dermatitis exacerbations [82, 83]. Multiple therapeutic modalities exist, but no monotherapy has proven exceptional in ameliorating the symptoms of this disease. Current topical and systemic therapeutic options offer benefit but carry varying degrees of adverse effects that often limit their application.

There are several reports on anti-IgE therapy in patients with atopic eczema [84-86] and although some describe favourable treatment results [87] these are not consistently reported in all studies [88].

Food Allergies

Up to 6% of young children and 2% of adults suffer from food allergy [89]. Among them many have IgE-mediated food allergy, a condition with potentially fatal allergic reactions. The only proven treatment is avoidance of the offending food, which can be identified using standardised allergic tests. However, several studies have addressed possible definite treatment options for food allergy. Immunotherapy, administered orally or by systemic injections, shows promising preliminary results, but these therapeutics are based on studies with insufficient scientific support, or are associated with a high risk of severe side effects. Promising results were recently published with anti-IgE antibodies in a human trial [90]. A phase II clinical trial with omalizumab, was recently initiated in subjects with peanut allergy, but was stopped as a result of safety concerns after severe reactions occurred during initial oral challenges [91]. However, Donald *et al.* report significant decrease in peanut allergy sensitivity on oral food challenge with the use of 450mg dose of TNX-901 (Tanox, Houston, Texas, USA) a humanized IgG1 monoclonal antibody binding to the CH3 domain of IgE [92].

Occupational Allergies

Latex allergy is reported to affect 4.32% (range, 4.01% to 4.63%) of health care workers and 1.37% (range, 0.43% to 2.31%) of the general population [93]. Latex sensitivity is reported in 40% of children with spine bifida [94] as well as in those with fruit and vegetable allergy that are known to cross-react with latex [95].

Successful treatment with omalizumab in health care workers with latex allergy resulted in decreased IgE levels and improvement in symptoms score [18, 96].

Ocular Allergies

Conjunctival and corneal manifestations of atopic keratoconjunctivitis (AKC) are chronic, disabling and may be blinding. In common with other allergic diseases, such as asthma and atopic dermatitis, AKC is characterised by an allergen-induced immune response mediated through expression of IgE. Given the pivotal role of IgE in the allergic cascade, it is hypothesised that omalizumab has potential as an entirely new therapeutic approach to AKC [67, 97].

Mastocytosis

Mastocytosis is a primary, abnormal accumulation of mast cells associated with a broad range of local and systemic symptoms. As a result patients may experience symptoms related to mast cell mediator release [98, 99]. A WHO consensus classification for mastocytosis exists, which is widely accepted and includes three major categories: (1) Cutaneous mastocytosis (CM), a benign disease in which MC infiltration is confined to the skin, is preferentially seen in young children and exhibits a marked tendency to regress spontaneously. (2) Systemic mastocytosis (SM) which is commonly diagnosed in adults and includes: indolent SM (ISM, the most common form involving mainly skin and bone marrow); SM with an associated non-mast cell clonal hematological disease (SM-AHNMD); aggressive SM usually presenting without skin lesions, and MC leukemia (3) Extracutaneous mastocytoma which presents as a localized extracutaneous malignant or a benign tumor [100]. IgE binding to mast cells serves not only to sensitize them but also to promote their survival. Thus, neutralizing IgE may lead to reduction of mast cell numbers [15]. Accordingly, it was reported that high omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis [101] and that it improves symptoms in a patient with cutaneous mastocytosis [102].

Eosinophil-Associated Gastrointestinal Disorders (EGIDs)

EGID are commonly associated with atopy and are being recognized with increasing frequency. Current therapy for EGIDs is inadequate. Omalizumab treatment is associated with significantly decreased basophil and dendritic cell FcεRI expression and free IgE levels. Omalizumab increased the concentration of allergen required to trigger half-maximal basophil activation by 170-fold. Allergen skin test wheal and erythema responses decreased by 78% and 82%, respectively. Symptom scores were decreased although esophageal eosinophil counts remained unchanged. These results suggest that IgE-mediated processes contribute to the

generation of eosinophilic inflammation in EGIDs and that anti-IgE therapy might be effective in these disorders [103].

Immunotherapies

The advantage of specific immunotherapy (SIT) is the potential to alter the course of the disease, which has been demonstrated in patients with allergic rhinitis, insect venom allergy and, to a lesser degree, asthma. The broader application of SIT is restricted by sometimes life-threatening adverse effects. The combination of anti-IgE with SIT was suggested to be superior to each single treatment protocol in children and adolescents with allergic rhinitis. In a randomized, double-blind trial to assess the efficacy and safety of anti-IgE (omalizumab) or placebo in combination with SIT (birch pollen or grass pollen), the combination therapy reduced symptom load, the sum of daily symptom severity score plus rescue medication use, over the birch and grass pollen seasons by nearly 50% over SIT alone [104-107]. Similarly, the combination of anti-IgE (omalizumab) therapy with ragweed injection immunotherapy for seasonal allergic rhinitis results in a significant reduction in systemic side effects and enhanced efficacy compared with immunotherapy alone. One proposed mechanism of immunotherapy is to induce regulatory antibodies that inhibit facilitated antigen presentation. Allergen-specific IgG4 levels were only increased after immunotherapy, both in the presence and absence of anti-IgE treatment. Combined treatment resulted in the induction of long-lasting inhibitory antibody function for up to 42 weeks compared with either treatment alone [108]. The advantage treatment combining SIT with omalizumab has been reported also in a case of beekeepers anaphylaxis [109].

Ménière's Disease

Ménière's disease (MD) is a complex, multifactorial disorder of the inner ear that is the most common cause of the syndrome of episodic vertigo with fluctuating hearing loss [110]. There is evidence for a probable role of IgE in the production of the symptoms of Meniere's disease. The endolymphatic sac is the seat of immune reactivity in the inner ear. Inhalant and food allergies have been linked with symptoms of Meniere's disease, and many of the clinical characteristics of Meniere's disease suggest an underlying autoimmune etiology [111]. Successful treatment of Ménière disease with anti-IgE therapy has been recently reported [102].

Safety Profile

Omalizumab is reported to have a favourable safety profile similar to placebo with few side effects [112].

Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma are reported [113,114]. Intubation secondary to asthma exacerbation in a patient with asthma receiving omalizumab was also reported [115].

The rate of anaphylaxis in post marketing surveillance surveys is 0.2% [116] The Omalizumab Joint Task Force (OJTF) concluded that 35 patients had 41 episodes of anaphylaxis associated with Xolair (omalizumab) administration between June 1, 2003, and December 31, 2005. Of those 36 events for which the time of reaction was known,

22 (61%) reactions occurred in the first 2 hours after one of the first 3 doses. Five (14%) of the events after the fourth or later doses occurred within 30 minutes [117,118]. The anaphylaxis might be caused by polysorbate that is an excipient in omalizumab [119].

Another rare association with omalizumab treatment is the occurrence of Churge-Strauss vasculitis [120,121]. In trials reported to the FDA twice as many patients receiving omalizumab had malignancies [59]. However, given that there were no trends for a specific tumor type, that malignancy was diagnosed early in the first 26 weeks of treatment and that the control group had lower rates of malignancy compared to normal, it is unlikely related to omalizumab treatment. Furthermore, an expert panel of oncologists who blindly reviewed the cases concluded that the malignancies either existed prior to the study, were unrelated or remotely related to the study drug [112].

There is concern that therapeutic antibodies that neutralize IgE (anti-IgE) may be unsafe in subjects at risk of helminth infection. In an exploratory study of allergic subjects at high risk of helminth infections, omalizumab therapy appeared to be safe and well tolerated, might have been associated with a modest increase in the incidence of geohelminth infection. However, infection severity and response to anthelmintics appeared to be unaffected by omalizumab therapy [122]. Lanzavecchia *et al.* discloses an invention related to neutralising antibodies which are specific for human cytomegalovirus and bind with high affinity as well as immortalised B cells that produce such antibodies. The antibodies of the invention also have a high potency for the neutralisation of infection [123].

TREATMENT RECOMMENDATIONS

Omalizumab is available since 2003 and is recommended as an adjunctive therapy for adults and adolescents (≥ 12 years) with moderate to severe persistent asthma who have a positive skin prick test or *in vivo* reactivity to perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids [116]. Thus initiating omalizumab treatment requires measurement of total IgE and a positive test to perennial allergen. The dose and frequency (every 2 to 4 weeks) are based on initial serum total IgE level and body weight [124]. Total IgE levels during treatment initiation are not informative as omalizumab forms complexes with IgE that have a slower elimination time from blood compared to free IgE. Thus, doses are based on serum IgE obtained prior to treatment initiation [112, 125]. The drug is administered subcutaneously and reaches peak serum levels 7-8 days after drug administration. A decrease of free serum levels of IgE of more than 96% is achieved within 1 hour after the first dose and is maintained between doses [112].

In July 3, 2007, the FDA (Food and Drug Administration) added a boxed warning to the labelling of omalizumab addressing the risk of an anaphylactic reaction [126].

Considering the timing of anaphylactic events, an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections would capture 75% of the anaphylactic reactions. The Omalizumab Joint Task Force

(OJTF) report provides recommendations for physicians who prescribe omalizumab on (1) the suggested wait periods after administration and (2) patient education regarding anaphylaxis [59, 117]. The National Asthma Education and Prevention Program (NAEPP) panel advises that clinician administering omalizumab should be prepared and equipped for identification and treatment of anaphylaxis [118].

CURRENT & FUTURE DEVELOPMENTS

Recent studies suggest high or increasing prevalence of allergic disorders including asthma, eczema and food allergies [127-129]. Allergic rhinitis is one of the most common presentations of allergic disorders in the United States, affecting more than 20% of the population [130] and estimates of the prevalence of asthma range from 7% in France and Germany to 11% in the USA and 15-18% in the United Kingdom [53]. Allergic asthma and rhinitis imposes a huge burden in terms of treatment costs, productivity loss and hospital admissions. Given that IgE is a pivotal molecule in the pathogenesis of these diseases and possibly in other traditionally non-atopic processes, it is likely that drugs targeting IgE such as omalizumab will gain increased importance in clinical practice. It is also possible that earlier use of omalizumab in atopic patients, due to its effects on inflammation in general and IgE mediated processes in particular [131], may have favourable effects on the natural course of atopic diseases such as asthma, allergic skin disease, food allergies, eye and gastrointestinal diseases. Furthermore, through omalizumab treatment better control of concomitant atopic diseases, regardless of the type of allergic sensitisation can be achieved. Finally, other future developments may involve combination treatments. This is exemplified by Currie that discloses the use of chymotrypsin inhibitors in combination therapy with recombinant humanized monoclonal antibody e.g. omalizumab in the treatment of respiratory and other disorders [132] and Kang *et al.* that discloses the use of 4-IBBL blocking agents in combination with anti-inflammatory medication for example, Adalimumab, Efalizumab, and Omalizumab for reducing sustained production of tumour necrosis factor [133]. Further studies are required in order to determine the contribution of omalizumab to the treatment of non-atopic processes in which IgE might play a role.

REFERENCES

- [1] Busse WW, Coffman RL, Gelfand EW, Kay AB, Rosenwasser LJ. Mechanisms of persistent airway inflammation in asthma. A role for T cells and T-cell products. *Am J Respir Crit Care Med* 1995; 152(1): 388-393.
- [2] Busse WW. Inflammation in asthma: The cornerstone of the disease and target of therapy. *J Allergy Clin Immunol* 1998; 102(4 Pt 2): S17-S22.
- [3] Johansson SG, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology* 1967; 13(4): 381-394.
- [4] Bennich H, Ishizaka K, Ishizaka T, Johansson SG. A comparative antigenic study of gamma E-globulin and myeloma-IgND. *J Immunol* 1969; 102(4): 826-831.
- [5] Ishizaka T, Ishizaka K. Biology of immunoglobulin E. Molecular basis of reaginic hypersensitivity. *Prog Allergy* 1975; 19: 60-121.
- [6] Hellman L. Regulation of IgE homeostasis, and the identification of potential targets for therapeutic intervention. *Biomed Pharmacother* 2007; 61(1): 34-49.
- [7] Sha WC, Liou HC, Tuomanen EI, Baltimore D. Targeted disruption of the p50 subunit of NF-kappa B leads to multifocal defects in immune responses. *Cell* 1995; 80(2): 321-330.

- [8] Chen CL, Yull FE, Cardwell N, *et al.* RAG2-/-, I kappa B-alpha/- chimeras display a psoriasisiform skin disease. *J Invest Dermatol* 2000; 115(6): 1124-1133.
- [9] Messner B, Stutz AM, Albrecht B, Peiritsch S, Woitschlag M. Cooperation of binding sites for STAT6 and NF kappa B/rel in the IL-4-induced up-regulation of the human IgE germline promoter. *J Immunol* 1997; 159(7): 3330-3337.
- [10] Harris MB, Mosteck J, Rothman PB. Repression of an interleukin-4-responsive promoter requires cooperative BCL-6 function. *J Biol Chem* 2005; 280(13): 13114-13121.
- [11] Harris MB, Chang CC, Berton MT, *et al.* Transcriptional repression of Stat6-dependent interleukin-4-induced genes by BCL-6: Specific regulation of iepsilon transcription and immunoglobulin E switching. *Mol Cell Biol* 1999; 19(10): 7264-7275.
- [12] Yokota Y, Mansouri A, Mori S, *et al.* Development of peripheral lymphoid organs and natural killer cells depends on the helix-loop-helix inhibitor Id2. *Nature* 1999; 397(6721): 702-706.
- [13] Metzger H. The receptor with high affinity for IgE. *Immunol Rev* 1992; 125: 37-48.
- [14] Turner H, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonRI. *Nature* 1999; 402(6760): B24-B30.
- [15] Kawakami T, Galli SJ. Regulation of mast-cell and basophil function and survival by IgE. *Nat Rev Immunol* 2002; 2(10): 773-786.
- [16] Gounni AS, Lamkhioed B, Ochiai K, *et al.* High-affinity IgE receptor on eosinophils is involved in defence against parasites. *Nature* 1994; 367(6459): 183-186.
- [17] Zhang M, Murphy RF, Agrawal DK. Decoding IgE Fc receptors. *Immunol Res* 2007; 37(1): 1-16.
- [18] Owen CE. Immunoglobulin E: Role in asthma and allergic disease: Lessons from the clinic. *Pharmacol Ther* 2007; 113(1): 121-133.
- [19] Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (Omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001; 164(8 Pt 2): S6-11.
- [20] Hakonarson H, Carter C, Kim C, Grunstein MM. Altered expression and action of the low-affinity IgE receptor FcepsilonRII (CD23) in asthmatic airway smooth muscle. *J Allergy Clin Immunol* 1999; 104(3 Pt 1): 575-584.
- [21] Kehry MR, Yamashita LC. Low-affinity IgE receptor (CD23) function on mouse B cells: role in IgE-dependent antigen focusing. *Proc Natl Acad Sci USA* 1989; 86(19): 7556-7560.
- [22] Borish L, Williams J, Johnson S, Mascali JJ, Miller R, Rosenwasser LJ. Anti-inflammatory effects of nedocromil sodium: inhibition of alveolar macrophage function. *Clin Exp Allergy* 1992; 22(11): 984-990.
- [23] Presta L, Shields R, O'Connell L, *et al.* The binding site on human immunoglobulin E for its high affinity receptor. *J Biol Chem* 1994; 269(42): 26368-26373.
- [24] Holowka D, Gosse JA, Hammond AT, *et al.* Lipid segregation and IgE receptor signaling: a decade of progress. *Biochim Biophys Acta* 2005; 1746(3): 252-259.
- [25] Holowka D, Sil D, Torigoe C, Baird B. Insights into immunoglobulin E receptor signaling from structurally defined ligands. *Immunol Rev* 2007; 217: 269-279.
- [26] Young RM, Holowka D, Baird B. A lipid raft environment enhances Lyn kinase activity by protecting the active site tyrosine from dephosphorylation. *J Biol Chem* 2003; 278(23): 20746-20752.
- [27] On M, Billingsley JM, Jouvin MH, Kinet JP. Molecular dissection of the FcRbeta signaling amplifier. *J Biol Chem* 2004; 279(44): 45782-45790.
- [28] Dombrowicz D, Lin S, Flamand V, Brini AT, Koller BH, Kinet JP. Allergy-associated FcRbeta is a molecular amplifier of IgE- and IgG-mediated *in vivo* responses. *Immunity* 1998; 8(4): 517-529.
- [29] Kurosaki T, Okada T. Regulation of phospholipase C-gamma2 and phosphoinositide 3-kinase pathways by adaptor proteins in B lymphocytes. *Int Rev Immunol* 2001; 20(6): 697-711.
- [30] Harmer SL, DeFranco AL. Shc contains two Grb2 binding sites needed for efficient formation of complexes with SOS in B lymphocytes. *Mol Cell Biol* 1997; 17(7): 4087-4095.
- [31] Davis RJ. Transcriptional regulation by MAP kinases. *Mol Reprod Dev* 1995; 42(4): 459-467.
- [32] Song JS, Haleem-Smith H, Arudchandran R, *et al.* Tyrosine phosphorylation of Vav stimulates IL-6 production in mast cells by a Rac/c-Jun N-terminal kinase-dependent pathway. *J Immunol* 1999; 163(2): 802-810.
- [33] Lee YN, Tuckerman J, Nechushtan H, Schutz G, Razin E, Angel P. c-Fos as a regulator of degranulation and cytokine production in FcepsilonRI-activated mast cells. *J Immunol* 2004; 173(4): 2571-2577.
- [34] Williams CM, Galli SJ. The diverse potential effector and immunoregulatory roles of mast cells in allergic disease. *J Allergy Clin Immunol* 2000; 105(5): 847-859.
- [35] Brown JM, Wilson TM, Metcalfe DD. The mast cell and allergic diseases: role in pathogenesis and implications for therapy. *Clin Exp Allergy* 2008; 38(1): 4-18.
- [36] Williams CM, Galli SJ. Mast cells can amplify airway reactivity and features of chronic inflammation in an asthma model in mice. *J Exp Med* 2000; 192(3): 455-462.
- [37] Kobayashi T, Miura T, Haba T, *et al.* An essential role of mast cells in the development of airway hyperresponsiveness in a murine asthma model. *J Immunol* 2000; 164(7): 3855-3861.
- [38] Breedveld FC. Therapeutic monoclonal antibodies. *Lancet* 2000; 355(9205): 735-740.
- [39] Presta LG, Lahr SJ, Shields RL, *et al.* Humanization of an antibody directed against IgE. *J Immunol* 1993; 151(5): 2623-2632.
- [40] Chang TW. The pharmacological basis of anti-IgE therapy. *Nat Biotechnol* 2000; 18(2): 157-162.
- [41] Shields RL, Whether WR, Zionscheck K, *et al.* Inhibition of allergic reactions with antibodies to IgE. *Int Arch Allergy Immunol* 1995; 107(1-3): 308-312.
- [42] Berger P, Scotto-Gomez E, Molimard M, Marthan R, Le G, Tunon-de-Lara JM. Omalizumab decreases nonspecific airway hyperresponsiveness *in vitro*. *Allergy* 2007; 62(2): 154-161.
- [43] MacGlashan DW Jr, Bochner BS, Adelman DC, *et al.* Down-regulation of Fc(epsilon)RI expression on human basophils during *in vivo* treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997; 158(3): 1438-1445.
- [44] Plevako H, Arvidsson M, Petruson K, *et al.* The effect of omalizumab on nasal allergic inflammation. *J Allergy Clin Immunol* 2002; 110(1): 68-71.
- [45] Malveaux FJ, Conroy MC, Adkinson NF Jr, Lichtenstein LM. IgE receptors on human basophils. Relationship to serum IgE concentration. *J Clin Invest* 1978; 62(1): 176-181.
- [46] Gomez G, Jogie-Brahim S, Shima M, Schwartz LB. Omalizumab reverses the phenotypic and functional effects of IgE-enhanced Fc epsilonRI on human skin mast cells. *J Immunol* 2007; 179(2): 1353-1361.
- [47] Dreyfus DH. Observations on the mechanisms of omalizumab as a steroid-sparing agent in autoimmune or chronic idiopathic urticaria and angioedema. *Ann Allergy Asthma Immunol* 2008; 100(6): 624-5.
- [48] Noga O, Hanf G, Kunkel G, Kleine-Tebbe J. Basophil histamine release decreases during omalizumab therapy in allergic asthmatics. *Int Arch Allergy Immunol* 2008; 146(1): 66-70.
- [49] Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 2003; 112(2): 252-262.
- [50] Humbert M, Durham SR, Ying S, *et al.* IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: Evidence against "intrinsic" asthma being a distinct immunopathologic entity. *Am J Respir Crit Care Med* 1996; 154(5): 1497-1504.
- [51] Humbert M, Grant JA, Taborda-Barata L, *et al.* High-affinity IgE receptor (FcepsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma. *Am J Respir Crit Care Med* 1996; 153(6 Pt 1): 1931-1937.
- [52] Ying S, Humbert M, Meng Q, *et al.* Local expression of epsilon germline gene transcripts and RNA for the epsilon heavy chain of IgE in the bronchial mucosa in atopic and nonatopic asthma. *J Allergy Clin Immunol* 2001; 107(4): 686-692.
- [53] Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: A review of the prevalence, disease burden and options for treatment. *Respir Med* 2006; 100(7): 1139-1151.
- [54] Thompson PJ, Misso NL, Woods J. Omalizumab (Xolair) in patients with steroid-resistant asthma: Lessons to be learnt. *Respirology* 2007; 12 (3): S29-S34.
- [55] Fahy JV, Fleming HE, Wong HH, *et al.* The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 155(6): 1828-1834.
- [56] Gibson PG, Taramcaz P, McDonald VM. Use of omalizumab in a severe asthma clinic. *Respirology* 2007; 12 (3): S35-S44.

- [57] Buhl R, Soler M, Matz J, *et al.* Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J* 2002; 20(1): 73-78.
- [58] Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: A pooled analysis. *Curr Med Res Opin* 2007; 23(10): 2379-2386.
- [59] National Asthma education and Prevention program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health; National Heart, Lung and Blood institute; 2007. Publication No. 07-4051: 225-226.
- [60] Rapaka RR, Kolls JK. Pathogenesis of allergic bronchopulmonary aspergillosis in cystic fibrosis: Current understanding and future directions. *Med Mycol* 2008; 1-7. [Epub ahead of print].
- [61] van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax* 2007; 62(3): 276-277.
- [62] Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987; 79(5): 683-688.
- [63] Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: A whole population birth cohort study. *Pediatrics* 2001; 108(2): E33.
- [64] Krouse JH. The unified airway--conceptual framework. *Otolaryngol Clin North Am* 2008; 41(2): 257-266.
- [65] Magnan A, Meunier JP, Sagnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: A French observational cross-sectional study. *Allergy* 2008; 63(3): 292-298.
- [66] Demoly P, Bousquet PJ. Links between allergic rhinitis and asthma still reinforced. *Allergy* 2008; 63(3): 251-254.
- [67] Nagakura T, Ogino S, Okubo K, Sato N, Takahashi M, Ishikawa T. Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Clin Exp Allergy* 2008; 38(2): 329-337.
- [68] Morjaria JB, Gnanakumaran G, Babu KS. Anti-IgE in allergic asthma and rhinitis: an update. *Expert Opin Biol Ther* 2007; 7(11): 1739-1747.
- [69] Casale TB, Condemni J, LaForce C, *et al.* Effect of omalizumab on symptoms of seasonal allergic rhinitis: A randomized controlled trial. *JAMA* 2001; 286(23): 2956-2967.
- [70] Grundmann SA, Hemfort PB, Luger TA, Brehler R. Anti-IgE (omalizumab): A new therapeutic approach for chronic rhinosinusitis. *J Allergy Clin Immunol* 2008; 121(1): 257-258.
- [71] Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. *Am J Rhinol* 2007; 21(4): 428-432.
- [72] Zuberbier T, Bindslev-Jensen C, Canonica W, *et al.* EAACI/GA2LEN/EDF guideline: Definition, classification and diagnosis of urticaria. *Allergy* 2006; 61(3): 316-320.
- [73] Greaves MW, Tan KT. Chronic urticaria: Recent advances. *Clin Rev Allergy Immunol* 2007; 33(1-2): 134-143.
- [74] Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2007; 99(2): 190-193.
- [75] Sheikh J. Effect of omalizumab on patients with chronic urticaria: Issues with the determination of autoimmune urticaria. *Ann Allergy Asthma Immunol* 2008; 100(1): 88-89.
- [76] Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy* 2008; 63(2): 247-249.
- [77] Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol* 2006; 117(6): 1415-1418.
- [78] Temino VM, Peebles RS. The spectrum and treatment of angioedema. *Am J Med* 2008; 121(4): 282-286.
- [79] Krishnamurthy A, Naguwa SM, Gershwin ME. Pediatric angioedema. *Clin Rev Allergy Immunol* 2008; 34(2): 250-259.
- [80] Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. *J Allergy Clin Immunol* 2007; 120(4): 979-981.
- [81] Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008; 121(6): 1337-1343.
- [82] Ponyai G, Hidvegi B, Nemeth I, Sas A, Temesvari E, Karpati S. Contact and aeroallergens in adulthood atopic dermatitis. *J Eur Acad Dermatol Venereol* 2008. [Epub ahead of print]
- [83] Dai YS. Allergens in atopic dermatitis. *Clin Rev Allergy Immunol* 2007; 33(3): 157-166.
- [84] Belloni B, Ziai M, Lim A, *et al.* Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. *J Allergy Clin Immunol* 2007; 120(5): 1223-1225.
- [85] Forman SB, Garrett AB. Success of omalizumab as monotherapy in adult atopic dermatitis: Case report and discussion of the high-affinity immunoglobulin E receptor, FcepsilonRI. *Cutis* 2007; 80(1): 38-40.
- [86] Andres C, Belloni B, Mempel M, Ring J. Omalizumab for patients with severe and therapy-refractory atopic eczema? *Curr Allergy Asthma Rep* 2008; 8(3): 179-180.
- [87] Lane JE, Cheyney JM, Lane TN, Kent DE, Cohen DJ. Treatment of recalcitrant atopic dermatitis with omalizumab. *J Am Acad Dermatol* 2006; 54(1): 68-72.
- [88] Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. *J Am Acad Dermatol* 2005; 53(2): 338-340.
- [89] Rona RJ, Keil T, Summers C, *et al.* The prevalence of food allergy: A meta-analysis. *J Allergy Clin Immunol* 2007; 120(3): 638-646.
- [90] Rance F. Promising treatments in development for food allergies. *Expert Opin Emerg Drugs* 2004; 9(2): 257-268.
- [91] Chehade M. IgE and non-IgE-mediated food allergy: Treatment in 2007. *Curr Opin Allergy Clin Immunol* 2007; 7(3): 264-268.
- [92] Leung DY, Sampson HA, Yunginger JW, *et al.* Effects of anti-IgE therapy in patients with peanut allergy. *N Engl J Med.* 2003; 348(11): 986-993.
- [93] Bousquet J, Flahault A, Vandenplas O, *et al.* Natural rubber latex allergy among health care workers: A systematic review of the evidence. *J Allergy Clin Immunol* 2006; 118(2): 447-454.
- [94] Ausili E, Tabacco F, Focarelli B, Nucera E, Patriarca G, Rendeli C. Prevalence of latex allergy in spina bifida: Genetic and environmental risk factors. *Eur Rev Med Pharmacol Sci* 2007; 11(3): 149-153.
- [95] Rolland JM, O'Hehir RE. Latex allergy: A model for therapy. *Clin Exp Allergy* 2008; 38(6): 898-912.
- [96] Leynadier F, Doudou O, Gaouar H, *et al.* Effect of omalizumab in health care workers with occupational latex allergy. *J Allergy Clin Immunol* 2004; 113(2): 360-361.
- [97] Williams PB, Sheppard JD Jr. Omalizumab: A future innovation for treatment of severe ocular allergy? *Expert Opin Biol Ther* 2005; 5(12): 1603-1609.
- [98] Ben AD, Metzker A, Cohen HA. Pediatric cutaneous mastocytosis: A review of 180 patients. *Isr Med Assoc J* 2005; 7(5): 320-322.
- [99] Valent P, Horny HP, Escribano L, *et al.* Diagnostic criteria and classification of mastocytosis: A consensus proposal. *Leuk Res* 2001; 25(7): 603-625.
- [100] Horny HP, Sotlar K, Valent P. Mastocytosis: State of the art. *Pathobiology* 2007; 74(2): 121-132.
- [101] Kontou-Fili K. High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis. *Allergy* 2008; 63(3): 376-378.
- [102] Siebenhaar F, Kuhn W, Zuberbier T, Maurer M. Successful treatment of cutaneous mastocytosis and Meniere disease with anti-IgE therapy. *J Allergy Clin Immunol* 2007; 120(1): 213-215.
- [103] Foroughi S, Foster B, Kim N, *et al.* Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin Immunol* 2007; 120(3): 594-601.
- [104] Stock P, Rolinck-Werninghaus C, Wahn U, Hamelmann E. The role of anti-IgE therapy in combination with allergen specific immunotherapy for seasonal allergic rhinitis. *BioDrugs* 2007; 21(6): 403-410.
- [105] Bez C, Schubert R, Kopp M, *et al.* Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy* 2004; 34(7): 1079-1085.
- [106] Chervinsky P, Casale T, Townley R, *et al.* Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; 91(2): 160-167.
- [107] Casale TB, Busse WW, Kline JN, *et al.* Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006; 117(1): 134-140.

- [108] Klunker S, Saggar LR, Seyfert-Margolis V, *et al.* Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: Inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol* 2007; 120(3): 688-695.
- [109] Schulze J, Rose M, Zielen S. Beekeepers anaphylaxis: successful immunotherapy covered by omalizumab. *Allergy* 2007; 62(8): 963-964.
- [110] Gates GA. Meniere's disease review 2005. *J Am Acad Audiol* 2006; 17(1): 16-26.
- [111] Di Berardino F, Barozzi S, Cesarani A. Allergy and Meniere's disease: a review. *Eur Ann Allergy Clin Immunol* 2005; 37(8): 299-300.
- [112] Kuhn R. Immunoglobulin E blockade in the treatment of asthma. *Pharmacotherapy* 2007; 27(10): 1412-1424.
- [113] Omalizumab: Anaphylactic shock: sometimes occurs more than one hour after the injection. *Prescrire Int* 2008; 17(93): 22.
- [114] Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007; 120(6): 1378-1381.
- [115] Jacobs ZD, Guajardo JR. Intubation secondary to asthma exacerbation in a patient with asthma receiving Xolair (omalizumab). *Pediatr Pulmonol* 2008; 43(1): 102-103.
- [116] Prenner BM. Asthma 2008: Targeting immunoglobulin E to achieve disease control. *J Asthma* 2008; 45(6): 429-436.
- [117] Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007; 120(6): 1373-1377.
- [118] Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007; 120(5): S94-138.
- [119] Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; 28(3): 313-319.
- [120] Bargagli E, Madioni C, Olivieri C, Penza F, Rottoli P. Churg-Strauss vasculitis in a patient treated with omalizumab. *J Asthma* 2008; 45(2): 115-116.
- [121] Ruppert AM, Averous G, Stanciu D, *et al.* Development of Churg-Strauss syndrome with controlled asthma during omalizumab treatment. *J Allergy Clin Immunol* 2008; 121(1): 253-254.
- [122] Cruz AA, Lima F, Sarinho E, *et al.* Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. *Clin Exp Allergy* 2007; 37(2): 197-207.
- [123] Lanzavecchia, A., Macagno, A.: WO08084410(2008).
- [124] Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004; 59(7): 701-708.
- [125] Hochhaus G, Brookman L, Fox H, *et al.* Pharmacodynamics of omalizumab: Implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin* 2003; 19(6): 491-498.
- [126] Kelly HW. Rationale for the major changes in the pharmacotherapy section of the National Asthma Education and Prevention Program guidelines. *J Allergy Clin Immunol* 2007; 120(5): 989-994.
- [127] Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: A 5-year follow-up study. *J Allergy Clin Immunol* 2003; 112(6): 1203-1207.
- [128] Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002; 110(5): 784-789.
- [129] Novak N, Bieber T, Leung DY. Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol* 2003; 112(6): S128-S139.
- [130] Bukstein DA, Lapine TJ. Allergic Rhinitis in Family Practice: The Role of Levocetirizine in Clinical Care. *Postgrad Med* 2008; 120(2): 101-110.
- [131] Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reinzer C. The anti-inflammatory effect of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005; 115: 459-465.
- [132] Currie, M.G.: US20080025966 (2008).
- [133] Kang, Y.J., Han, J.: WO08057171(2008).