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An Overview of the Effects of anti-IgE Therapies

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Omalizumab, a humanized mAb that binds to the CH3 domain near the binding site for the high-affinity type-I IgE Fc receptors of human IgE, can neutralize free IgE and inhibit the IgE allergic pathway without sensitizing mast cells and basophils. We found that omalizumab in patients with severe persistent asthma (SPA) was an effective therapy for asthma and the following co-morbid conditions: chronic urticaria (CU), bee venom allergy, latex allergy, atopic dermatitis, food allergy and Samter's syndrome. Information on the use of omalizumab in treatment of asthma and other allergic diseases has improved our understanding that treatment acts on many levels, including regulating levels of inflammatory proteins, including cytokines (copper-containing alpha- 2-glycoprotein, total antioxidant capacity, MDA, NO, H_2O_2, CXCL8, IL-10, TGF-β, GMCSF, IL-17, IL-1β), MPV, Hs-CRP, eosinophil cationic peptide, vitamin-D (25(OH)D), homocysteine (Hcy), OX-2, d- dimer, albumin, and sApo-2L. The decrease in Hcy concentrations and increase in 25(OH)D also support the existence of a vascular endothelial protection mechanism. Mediators and cells classically involved in pro-coagulant and anticoagulant pathways together play a role in SPA and CU pathophysiology and omalizumab effect.

The mechanism of action of omalizumab in the treatment of asthma is believed to be multifactorial, and includes effects mediated through altered production of redox metabolites, extrinsic coagulation pathway, oxidative markers-related mi RNA, TRAIL-related mi RNA, and regulation of production of known inflammatory proteins

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Background

Omalizumab – anti-immunoglobulin E (IgE) – is approved for the treatment of severe allergic asthma. In addition to asthma, Omalizumab has been investigated in various other conditions, including chronic urticaria (CU), perennial and seasonal allergic rhinitis (AR), latex allergy, peanut allergy, idiopathic anaphylaxis, hyper-IgE syndrome, chronic rhinosinusitis, interstitial cystitis, aspirin sensitivity, mastocytosis, eosinophilic gastroenteritis, and atopic dermatitis [1,2]. Omalizumab – a humanized mAb that binds to the CH3 domain near the binding site for the high-affinity type-I IgE Fc receptors of human IgE – can neutralize free IgE and inhibit the IgE allergic pathway without sensitizing mast cells and basophils. It is conceivable that mast cells residing in the nasal lining, lower airway, other areas of the mucosal tracts, and in the skin, differ in tryptase and chymase content, sensitivity, receptor regulation, and life span [3–8]. The development of Omalizumab therapy over the past 20 years provides an interesting example of the emergence of a conceptually new, biotechnology-produced pharmaceutical [8].

Omalizumab and IgE Receptors

The potential for Omalizumab to exert anti-inflammatory effects in patients with asthma arises from its ability to target the interaction between IgE and IgE receptors (FceRI and FceRII), thereby preventing inflammatory cell activation and interrupting a key step in the allergic inflammatory cascade. The effects of Omalizumab on IgE receptors have been reviewed previously [6–9]. Most asthmatic individuals respond satisfactorily to inhaled corticosteroids and β-adrenergic agonists; however, 5–10% of them have severe, persistent symptoms that respond poorly to such treatment. The introduction of Omalizumab as an add-on therapy for inadequately controlled moderate-to-severe or severe persistent allergic asthma (SPA) provided a valuable new treatment option for patients. Given the importance of anti-inflammatory therapy for control of SPA, it is important to determine the effects of omalizumab on markers of inflammation. The interaction between Omalizumab and free IgE interrupts a key step in the allergic inflammatory cascade, preventing IgE from binding to mast cells, basophils, and dendritic cells, and down-regulating IgE receptor expression on these inflammatory cells, thereby inhibiting degranulation and the release of inflammatory mediators [9–12].

Omalizumab has been approved in over 100 countries for treating patients with SPA. These pharmaceutical developments have validated the IgE pathway as an effective therapeutic target for treating IgE-mediated allergic disease. In Turkey, Omalizumab was approved in 2006 for treating patients 15 years and older with severe allergic asthma and a billing policy was issued by the Health Insurance Bureau in the same year. Since then approximately 600 patients with severe allergic asthma have been treated with Omalizumab in major medical centers, with response rates estimated to be ~80–95%. In Turkey, a small number of patients with other allergic conditions have also been treated with Omalizumab in off-label uses with generally good results. Except for 1 patient who had a temporary thrombocytopenia, there have been no changes of mean platelet volumes in severe asthma patients without cardiovascular risk [13–15].

Omalizumab Effects on sApo-2 L

A number of studies have shown that both the membrane-bound tumor necrosis factor-related apoptosis-inducing ligand (TRAIL: Apo-2L) and soluble TRAIL (sApo-2L) can induce apoptosis in a wide variety of tumor types by activating death receptors. sTRAIL is used as a marker for apoptosis. TRAIL (Apo-2L) is a transmembrane (type II) glycoprotein belonging to the TNF superfamily. The extracellular domain of TRAIL is homologous to that of other family members and has a homotrimeric subunit structure. Like TNF and FasL, sApo-2L also exists physiologically in a biologically active soluble homotrimeric form. An increase in eosinophil levels has been reported in allergic asthma, and is thought to reflect an increase in peripheral blood eosinophil survival promoted by Apo-2 L. The exact role of Apo-2 L *in vivo*, however, remains unknown. In our previous study we showed that soluble Apo-2 L levels in patients with severe persistent allergic asthma decreased after anti-IgE treatment using omalizumab. I think that omalizumab inhibited activation of the TRAIL related extrinsic apoptotic pathway and lowered soluble Apo-2 L level by blocking free IgE. I also believe that soluble Apo-2 L may have an important role in the relationship between IgE and the extrinsic pathway in endothelial cells. These results suggested that sApo-2L may act as a soluble effector molecule, and that the decrease in levels after omalizumab treatment may allow us to use this marker to monitor clinical improvement.

Combination Therapy with Omalizumab and Allergen Immunotherapy

Combination therapy with omalizumab and specific subcutaneous immunotherapy (SCIT) in patients with severe persistent asthma also suggest that omalizumab is an effective therapy in such individuals. Omalizumab reduces serum IgE levels and FceRI receptor expression on key cells in the inflammatory cascade. The consequences of these processes are the inhibition of the release of inflammatory mediators from mast cells, and diminished recruitment of inflammatory cells, especially eosinophils, into the airways [11,16–18].

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Allergen-specific immunotherapy (SIT) has the advantage of being the only causal treatment of allergic controlled asthma and rhinitis but is fraught with the dangers of severe systemic or local adverse effects and anaphylaxis [19–21]. Allergic diseases are probably due to complex interactions between largely unknown genetic and environmental factors. The micro-array technique for the detection of specific IgE has improved the diagnostic procedures for allergic diseases. SIT has been used in the management of allergic diseases for nearly 100 years. The quality of allergen products is a key issue for both diagnosis and therapy. Between March 2009 and February 2013, we examined 5982 patients with allergic rhinoconjunctivitis and allergic asthma [22]. In our previous study, 1452 patients with symptoms and skin prick tests to +3 and +4 received SIT; 70% of the patients received SIT with mite and pollen mixtures due to the pollen in the air in the Mediterranean region. In patients who have allergic rhinoconjunctivitis and are treated with SIT (especially if there is atopic dermatitis), atopic dermatitis lesions in cases exacerbated by SIT may become generalized. This reaction is usually seen in the initial dose. In those cases, SIT should be discontinued [19]. A 16-year-old patient of ours with an allergic rhinoconjunctivitis developed a similar situation. The patient's complaints began 4 years previously. The patient's skin prick test was +4 positive with mite, +4 positive with olive, and +4 positive with *Parietaria judaica* (Judas tree). Blood level of total IgE was 645 IU / L. We planned SIT with the beginning at doses (ST allergens APSI, 2 numbered bottle, 5 doses). SIT was stopped due to exacerbation of skin lesions resistant to antihistamines and topical steroids. Omalizumab treatment started at a dose 375 mg every 2 weeks. After 2 months of treatment, when the skin lesions had been brought under control, we started SIT treatment again and this time no recurrence of the lesion was observed. This patient had taken omalizumab and SIT combination therapy for 3 years. Omalizumab can possibly overcome these limitations by binding exclusively to circulating IgE molecules and reducing the levels of circulating IgE, regardless of allergen specificity, by binding to the constant region of circulating IgE molecules. This prevents free IgE from interacting with the high- and low-affinity IgE receptors (Fc"RI and Fc"RII) on mast cells, basophils, macrophages, dendritic cells, and B lymphocytes, and subsequently leads to a decrease in the release of the mediators of the IgE mediated allergic response (i.e., cytokines, histamines, and leukotrienes) [23,24].

The first clinical trial looking for the clinical effects of a combined therapy of SIT and Omalizumab was performed in children and adolescents in Germany who were allergic to grass and birch pollen. Kuehr et al. recruited 221 children and adolescents to evaluate the efficacy and safety of omalizumab with SIT on birch pollen-induced allergic rhinitis (AR) [25]. SIT plus omalizumab-treated subjects were reported to have a 48% reduction in allergen-induced symptom load over 2 pollen seasons independent of the allergen. Furthermore, rescue medication use, number of days with symptoms, and symptom severity were significantly lower in the SIT plus omalizumab groups compared with SIT alone. A post hoc sub-analysis of this study to assess the effects of each treatment (SIT or omalizumab) demonstrated that SIT alone did not significantly reduce the symptom severity score [26]. Hence, combination therapy may be complimentary, providing superior effect compared to individual treatments. Recently, there have been trials of omalizumab and SIT in patients with AR and co-morbid asthma. In the trial by Kopp et al., a significant reduction of 40% in symptom load was observed in favor of SIT plus omalizumab compared with SIT alone (p=0.04) [27]. Another study showed that the tolerability of SIT after pretreatment with omalizumab or placebo in patients with symptomatic asthma was not adequately controlled with inhaled corticosteroids. A total of 13.5% of patients treated with Omalizumab showed systemic allergic reactions to SIT compared to 27% in those receiving placebo (p=0.017). More patients were able to reach the target maintenance SIT dose (p=0.004) in the omalizumab group compared to placebo [28], suggesting that pre-treatment with omalizumab was associated with fewer systemic allergic reactions to SIT and enabled more patients to achieve the target immunotherapy maintenance dose. Casale et al. examined the extent by which pre-treatment with omalizumab would be effective in enhancing efficacy of rush immunotherapy. The rush protocol intended a rapid increase in the allergen to provoke adverse effects of SIT. Pre-treatment with omalizumab resulted in a 5-fold reduction in anaphylactic reaction [29].

In a previously study we showed that 1 patient had previously reported honeybee-induced anaphylaxis. Interestingly, this patient, while on the 12th dose of omalizumab treatment, had 48 bee stings and developed only a slight local reaction, which resolved spontaneously. The results were in concordance with similar cases treated with omalizumab in the literature [15]. Although the effect of venom immunotherapy is well documented, there is also an increased risk of adverse effects ranging from itchy eyes an, sneezing to Jessner's lymphocytic infiltrate and severe anaphylaxis in bee venom-treated patients and in those with rapid dose increase [20]. This case suggests that omalizumab may be able to prevent severe anaphylaxis during immunotherapy.

Studies in patients with allergic rhinitis and asthma have shown that pre-treatment with omalizumab may be an effective option to safely reduce systemic anaphylactic reactions and achieve a higher dose of allergen immunotherapy. This may be of specific relevance to hymenoptera venom immunotherapy. Although there are no controlled trials, there are case reports of anti-IgE therapy with omalizumab reducing the risk of systemic reaction during induction of venom immunotherapy in patients who have either failed treatment or in those with mastocytosis [30–32].

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Omalizumab Effects on Oxidative Stress, Vitamin-D, and Homocysteine

Ceruloplasmin (CP) is a copper-containing alpha- 2-glycoprotein with a molecular weight of approximately 132 kDa. Ceruloplasmin is essential for iron homeostasis, is involved in angiogenesis, and under different conditions can act as either a pro- or anti-oxidant. The known functions of ceruloplasmin oxidase activity (COA) include copper transportation, iron metabolism, antioxidant defense, and involvement in angiogenesis and coagulation. It was previously reported that synthesis of CP was stimulated by interleukin-1 in normal and copper-deficient rat models concluding that CP was dependent on oxidase activity [33]. Moreover, the copper ions had been suggested as an explanation for the sensitivity of asthmatic individuals by biologic effects of inhaled particulate air pollution [34]. *In vivo* experiments searching for the cytokines involved in acute-phase protein response showed that there were 3 major cytokines: interleukin 1-beta, interleukin-6, and TNF-alpha [35].

The mechanisms underlying the clinical and anti-inflammatory efficacy of omalizumab are not fully understood. Omalizumab reduces airway inflammation, but few clinical trials shave studied the effect of this therapy on airway remodeling. Nitric oxide (NO) is an important biomarker for inflammation in airway epithelial cells and in the exhaled breath of asthmatic subjects. In our previous study we investigated changes in total antioxidant capacity in asthmatic patients treated with omalizumab. Anti-IgE therapy is an innovative and promising treatment modality that mediates its effects in part at least through decreased inflammation following improved anti-oxidant capability. In turn, our study suggested that measuring the latter may prove to be a useful surrogate marker to monitor efficacy of treatment in patients with this disease [36].

Alternatively, the development of atopy may also be a direct effect of elevated homocysteine or some of its metabolites, which appear to exert a number of diverse effects on immune function. In addition, total homocysteine (Hcy) has been shown to increase in response to immune activation and cell proliferation during a non-allergic Th1-type immune response. Although much less is known about the health effects of sustained post-load homocysteine concentrations, there is evidence that it has negative effects on platelet aggregation and endothelial function. A number of studies have indicated that homocysteine may contribute to the development and progression of atherosclerosis, a risk factor for cardiovascular diseases. However, the mechanisms by which Hcy can induce vascular dysfunction are not fully understood [38–43].

Vitamin-D (25(OH)D) has effects on the innate and adaptive immune system. 25(OH)D levels are associated with poor asthma control, reduced pulmonary function, increased medication intake, and exacerbations. Little is known about 25(OH)D in adult asthma patients or its association with asthma severity [44,45]. Moreover, 25(OH)D triggers an Hcy metabolizing enzyme and data from the Longitudinal Aging Study Amsterdam suggested a correlation between 25(OH)D status and Hcy levels [46]. The decrease in Hcy concentrations and increase in 25(OH)D also supports the existence of a vascular endothelial protection mechanism.

Omalizumab Effects on sCD200 (OX-2)

CD200 (OX-2) is a novel immune-effective molecule, both cell membrane-bound and also existing in a soluble form in serum (sCD200, sOX-2), which acts as a pro-inflammatory through its receptor [11,14,47]. In our previous study we reported a patient who had a pruritic bullous pemphigoid and very high levels of total IgE (5000 kU/L) who was refractory to the aggressive immunosuppressive regimens for bullous pemphigoid but responded rapidly to systemic anti-IgE. The circulating level of sOX-2 was 48.45 pg/mL in serum and 243 pg/mL in blister fluid. Soluble OX-2 levels were higher in blister fluid than in serum. During the second month of follow-up, the patient's sOX-2 level decreased to 26.7 pg/mL [48]. Reduction in serum levels sOX-2 with anti-IgE treatment suggests that sOX-2 could be pro-inflammatory [11,14,37,47,48]. Soluble OX-2 might also play a role in immune response in the pathogenesis of autoimmune and inflammatory skin disorders [50,51].

Omalizumab Effects on the Coagulation Pathway

We have observed 1 patient who underwent omalizumab treatment, who had severe persistent asthma (SPA) who had a history of protein C/S deficiency (who was also a heterozygous carrier of factor V Leiden and prothrombin G20210A mutation), multiple massive pulmonary embolus, and systemic subacute thrombosis determined in vena saphena parva and in left vena perforantes cruris. After long-term (20 months) treatment with omalizumab, he had decreased d-dimer (DD), sTRAIL, and OX-2, and had increased CXCL8, activated pC (APC), antithrombin III (AIII), protein S (pS), and protein C (pC) levels [11]. In this patient's blood, levels of APC, AIII, pS, and pC were found to be increased by 74%, 128%, 102%, and 86% respectively, and DD level (412 U/L) was decreased at the 30th month of omalizumab therapy, and these results were significant [12].

Severe persistent asthma, which is associated with a procoagulant state in the bronchoalveolar space, is further aggravated by impaired local activities of the anticoagulant pC/S, AIII system, and fibrinolysis, as demonstrated by massive fibrin depositions in the alveoli of a SPA patient, who died from a

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SPA attack, who did not respond to treatment. Recent reports revealed that patients with CU also show signs of thrombin generation and activation of the TF pathway of the coagulation system. DD, a fibrin degradation product formed during the lysis of a thrombus, is also detected in high levels in patients with active CU [52–56].

The biologic effects of APC and pC can be divided into anticoagulant and cytoprotective effects [53]. In patients with SPA, bronchoalveolar levels of APC decreased after a bronchial allergen challenge and were significantly lower than in healthy controls, and APC/pC ratios were decreased in induced sputum of patients with SPA, pointing to an imbalance between coagulation and the pC system [54].

Activation of the extrinsic pathway by TF generates thrombin, which leads to d-dimer formation [55]. We think that anti-IgE treatment with omalizumab inhibited activation of the extrinsic pathway and lowered d-dimer level by blocking free IgE. Because of this, we think that omalizumab has a similar effect as heparin. After the injection of heparin, an increase in the percentage of protein C/S has been observed.

Besides its anticoagulant properties, heparin possesses a wide range of anti-inflammatory activities, including inhibition of pro-inflammatory mediators, such as ECP, peroxidase, and neutrophil elastase, and inhibition of lymphocyte activation [58]. Anticoagulant treatment with heparin and warfarin had been attempted to reduce the symptoms of CU and SPA; however, inhaled heparin is no longer used in clinical practice as adjunctive therapy for SPA attacks because of equivocal results [55–57].

Because we considered the effect of omalizumab occurs in both the bronchial and systemic vascular areas, we evaluated SPA and CU patients before and after the therapy period. After omalizumab therapy, the significant decrease of the levels of DD shows the importance of the procoagulant state in allergic patients. We also believe that DD may have an important role in the relationship between IgE and the extrinsic pathway in endothelial cells. Mediators and cells classically involved in procoagulant and anticoagulant pathways together play a role in SPA and CU pathophysiology and omalizumab effect [12].

Omalizumab Effects on Hyperimmunoglobulin-E Syndrome, Eosinophilic Gastroenteritis, Mastocytosis, Chronic Urticaria, Atopic Dermatitis, Nasal Polyps, and Samter's Syndrome

The extrinsic pathway of coagulation is activated in response to a high level of circulatory IgE. The best example of this purported relationship is the correlation between higher TF expression and vasculitis degree seen in hyper IgE syndrome. Hyperimmunoglobulin E syndrome (HIES) is a heterogeneous group of immune disorders and is characterized by very high concentrations of the serum antibody IgE. Clinically eczema-like rash, cold staphylococcal infection, and severe lung infection are seen. An IgE level greater than 2000 IU/mL is often considered diagnostic except in patients younger than 6 months of age [59,60]. Abnormal neutrophil chemotaxis due to decreased production of interferon gamma by T lymphocytes is thought to cause the disease. Both autosomal dominant and recessive inheritance have been described. The autosomal dominant form of HIES results from mutations in STAT3 [59]. Mutations in the DOCK8 molecule have been associated with syndromes that share many features with classical autosomal dominant HIES, which is inherited by an autosomal recessive trait and tends to have a milder clinical picture [60,61]. STAT3 is a key regulator of many immunologic pathways and is involved in the signal transduction of many cytokines, including, but not limited to, IL-6, IL-10, IL-21, IL-22, and IL-23 [62]. Animals studies have shown that a myeloid-specific deletion of STAT3 leads to up-regulation of many Th1 cytokines, such as IFNγ and TNFα, and down-regulation of pro-inflammatory and anti-inflammatory responses regulated by IL-6 and IL-10, respectively [60,61]. These cytokines are critical to differentiation of TH17 cells, which are important in inflammatory response to bacterial and fungal pathogens. It was reported that both STAT3 mutation-positive and STAT3 mutation-negative HIES exhibited a profound deficit in TH17 differentiation [63]. Several studies reported clinical improvement in patients with severe atopic eczema with high serum IgE level [63–65].

Eosinophilic gastroenteritis (EGE) is characterized by patchy or diffuse eosinophilic infiltration of all parts of the gastrointestinal (GI) tract [66,67]. Eosinophils are normally present in gastrointestinal mucosa, but deeper infiltration and more than 30 eosinophils per high-power field in at least 5 areas are pathologic [68]. Since the GI tract is frequently faced with external allergens via ingested foods, allergens from food pass the mucosa and trigger an inflammatory response that leads mast cell degranulation and recruits eosinophils. Tissue damage is caused by cytotoxic proteins contained in the cytoplasmic granules of eosinophils. In addition to tissue eosinophils, eosinophils can also mediate proinflammatory effects such as up-regulation of adhesion systems, and modulation of cell trafficking, as well as release of chemokines (eotaxin), lipid mediators, and leukotriene. Eosinophil recruitment into the tissue is regulated by a number of inflammatory cytokines such as IL-3, IL-4, IL-5, IL-13, granulocyte macrophage colony stimulating factor (GM-CSF), and T helper 2 (Th2) cytokines. A Th2-type immune response seems to be involved in both IgE- and non-IgE-mediated EGE [69]. Anti-IgE treatment with omalizumab is associated with a 35–45% drop in peripheral blood eosinophil

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count, as well as a decrease in duodenal and antral eosinophil count [70,71]. It also effectively blocks CD23-mediated allergen binding to B cells. But some reports failed to demonstrate *in vivo* immunomodulatory activity on T cell responses [72].

Mastocytosis is a heterogeneous disorder that results from clonal mast cell proliferation (myeloproliferative neoplasm), characterized by excessive mast cell accumulation in skin (cutaneous form) or multiple tissues, with or without skin involvement (systemic form) [73,74]. Increased local concentration of soluble mast cell growth factors in lesions are believed to stimulate mast cell proliferation. Impaired mast cell apoptosis and interleukin 6 have also been postulated to be involved, as evidenced by BCL-2 up-regulation and IL-6 elevation in tissue. Some activating point mutations of c-kit in codon 816 (usually KITD816V), encoding the tyrosine kinase- receptor for stem cell factor, are found to be associated with the systemic form [75–77]. Since omalizumab reduces the expression of FcεRI on circulating basophils and mast cells, it seems to lower the activity potentials of basophils and mast cells, thereby reducing the potential reactivity of these cells [71,78]. Concordantly, serum tryptase was reported to decrease under omalizumab therapy in 2 mastocytosis patients, but it remained unchanged in 2 other patients [79].

Metz et al. [80] assessed responder rates, optimal dosage, response to up-/down-dosing, time to relief of symptoms, rates of return, and time of relapse after omalizumab administration, and safety in 51 CU patients, 20 with chronic spontaneous urticaria (CSU) alone, 21 with different forms of chronic inducible urticaria (CindU), and 10 with both in their clinical analysis. They showed that omalizumab is a rapidly acting, highly effective, and safe drug in CSU and CindU patients in their clinical experience from more than 1250 injections in those patients over 4 years. Their observations in a real-life clinical setting support the recommendation of the current EAACI/GA2LEN/EDF/WAO guideline for the management of urticaria to use omalizumab in the treatment of urticaria patients [81].

Omalizumab demonstrated clinical efficacy in the treatment of nasal polyps with comorbid asthma, supporting the importance and functionality of local IgE formation in the airways [82], but in our study, no change was seen in nasal polyposis after omalizumab treatment [14]. Nasal polyps from patients with Samter's triad had significantly higher inducible nitric oxide synthase activity compared with the nasal polyp patients without Samter's syndrome [83].

Severe refractory atopic dermatitis is a chronic, debilitating condition that is associated with elevated serum IgE levels. The mechanisms of omalizumab in the treatment of atopic dermatitis (AD) need further research in lowering serum IgE. Several case reports investigating anti-IgE therapy in patients with AD found symptomatic improvement with omalizumab [3]. Recently, Iyengar et al. [84] showed that all patients receiving omalizumab had strikingly decreased levels of TSLP, OX40L, TARC (involved in Th2 polarization) and interleukin-9 compared to placebo in their randomized, placebo-controlled clinical trial. In addition, they found a marked increase in IL-10, a tolerogenic cytokine, in the omalizumab-treated group. Patients on anti-IgE therapy had improved clinical outcomes.

Those patients who cannot be adequately controlled with even high doses of corticosteroids and often require repeated emergency visits and hospitalization are approved to use omalizumab by the health insurance systems in many countries [85–88]. We showed that omalizumab therapy increases blood glucose levels in allergic asthma patients with diabetes mellitus. Although we do not know the exact mechanism behind this relationship, it might be related to vial containing 145 mg sucrose [85].

Cost-Effectiveness Analysis of Omalizumab

Asthma affects over 300 million people around the world, particularly in the developing countries. It is seen in 5–10% of the population of developed countries and its prevalence is rising. More than 20 million people in the USA are estimated to have asthma [89]. Asthma markedly diminishes quality of life due to limited activity and absences from work or school and causes hospitalizations, with significant social and economic consequences [90,91].

Finally, regardless of the law and cost-effectiveness of omalizumab in a given WTP of $45 000 per QALY, it will remain its market position with the unique mechanism of action and great benefits to patients with severe asthma, particularly responders. However, the cost-effectiveness of omalizumab can be increased by confining omalizumab therapy to potential previous responders. However, caution is required to interpret the EVPI for omalizumab response, given the assumptions and the structural uncertainties. The reduction in the price of omalizumab is projected to improve the cost-effectiveness [92].

There have been concerns about cardiovascular safety in patients starting omalizumab therapy, because of the most recent study that analyzed the association between omalizumab and arterial thrombotic events [86–88,93]. We showed that in 1 of our patients, Doppler ultrasonography did not reveal any thrombus after anti-IgE therapy, the patient did not require lung transplantation, and serum protein S/C levels increased to normal ranges. The exercise stress testing result was normal and after initiation of anti-IgE treatment, and there were no cranial emboli events or any neurologic complications. Patients did not report any cardiac arrhythmias after initiation

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of anti-IgE therapy. Exercise stress testing results were normal while the patient was treated with anti-IgE. Aneurysm enlargement or complications were not detected during the treatment with anti-IgE [11].

Conclusions

In summary, omalizumab in patients with severe persistent asthma is an effective therapy for asthma and co-morbid conditions such as CU, bee venom allergy, latex allergy, multidrug allergy, atopic dermatitis, food allergy, Samter's syndrome. Since omalizumab therapy lowers the serum levels of soluble TRAIL [16,17], and soluble TRAIL was found to be correlated with survival in Stage 4 colon cancers [94–97], we do not propose omalizumab therapy for asthmatic patients with advanced colon cancer. The mechanism of action of omalizumab in the treatment of asthma is believed to be multifactorial, and includes effects mediated through altered production of redox metabolites, VEGF system, extrinsic coagulation pathway, oxidative markers related to mi RNA, TRAIL-related mi RNA, and regulation of production of known inflammatory proteins.

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