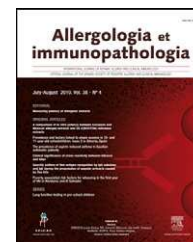


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REVIEW

Omalizumab beyond asthma

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Abstract

Introduction: Omalizumab has been demonstrated to be a successful therapy in the management of asthma through reduction of patient's symptoms and use of inhaled corticosteroids. The effect of omalizumab is achieved by immunoglobulin E (IgE) blockage and other secondary mechanisms resulting from this blockage. Because other diseases have an important IgE mediation in their physiopathology, the question arises as to if omalizumab would be useful in the treatment of other IgE-mediated diseases.

Objective: We present an overview of the experimental studies and clinical reports evaluating the use of omalizumab in diseases different to asthma including atopic dermatitis, urticaria, eosinophilic gastrointestinal disorders, idiopathic anaphylaxis, latex allergy, hymenoptera venom allergy, and other IgE diseases.

Methods: We reviewed the literature using PUBMED, EMBASE, and LILACS for publications which used omalizumab in the treatment of patients with allergic diseases or any other diseases. Complete articles published in English, Spanish or Portuguese were included.

Conclusion: There is not enough evidence to support the regular use of omalizumab in IgE diseases other than asthma. However, some experimental and clinical investigations indicate that omalizumab could be a therapeutic option in several allergic diseases like atopic dermatitis, urticaria, and eosinophilic gastrointestinal disorders. More control studies are needed in each IgE disease to evaluate the efficacy and safety of omalizumab in IgE mediated diseases.

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Mechanisms of action

Omalizumab is a humanised monoclonal antibody which selectively binds human immunoglobulin E. Previously it was designated as rhuMab-E2 and was also known as IgE-025. Omalizumab is an IgG protein containing a portion of human recombinant antibodies (95%) which constitute

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the immunoglobulin crystallisable fraction and is bound to a complementarity determining region originating from recombinant antibodies from a murid origin (5%). Omalizumab binds free IgE in its C ϵ 3 domain, and not through the crystallisable fraction of epsilon receptor 1 (Fc ϵ RI).¹ Macglashan et al. reported that omalizumab therapy for three months reduced the Fc ϵ RI receptors from about 220,000 to 8300 per basophile.² Lower stimulation of this receptor leads to a decrease in its expression within effectors cells such as mast cells, basophiles and dendritic cells (pDC1 and pDC2). It has been observed that reduction in free IgE and Fc ϵ RI leads to a decrease in allergens processing and their presentation to Th2 lymphocytes, along with a reduction in Th2 cells differentiation and lower expression of cytokines from this profile (IL-4, IL-5, IL-13). These changes could help to avoid new sensitisations to allergens and allergen-specific immune response.² Among the anti-inflammatory effects of omalizumab in asthma patients is the capacity to induce eosinophils apoptosis as well as the effect of reducing eosinophilia in sputum and bronchial biopsies.³ It has been

documented that the number of granulocyte-macrophage colony-stimulating factor (GM-CSF)-positive peripheral T lymphocytes decreases with the use of this humanised monoclonal antibody in addition to a significant reduction in the number of IL-2 and IL-13 positive T lymphocytes.⁴ Another anti-inflammatory effect occurs through reduction of the airway hyper-response to adenosine 5'-monophosphate.⁵ All these mechanisms of action are summarised in Fig. 1.

The clinical impact of omalizumab on the pathogenesis of asthma is reflected in a significant reduction of severe asthma exacerbation,⁶ mitigation of early and late response as measured by VEF1 recovery in both stages,⁷ significant reduction of inhaled corticosteroids doses,⁸ and improved quality of life rates.^{8,9}

The most common adverse reaction from omalizumab is pain as well as erythema in injection-site. However, warnings of anaphylaxis, malignancies, helminth infections, cardiovascular and cerebrovascular diseases have been reported. Review of spontaneous postmarketing adverse events submitted to the Food and Drug Administration (FDA)

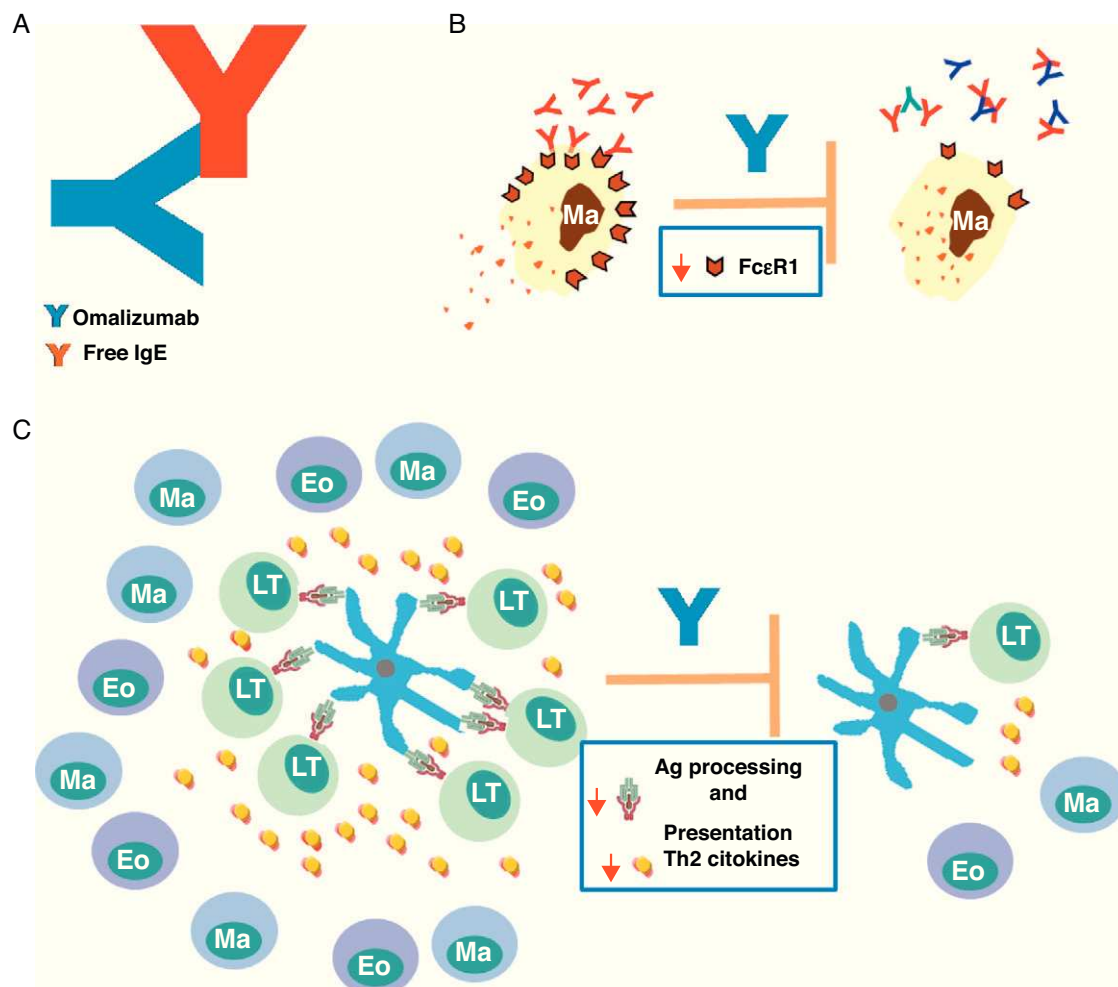


Figure 1 Mechanisms of action omalizumab in allergy diseases: omalizumab joined to free IgE (A). Lower stimulation of high affinity IgE receptor (Fc ϵ RI) leads to a decrease in its expression in mast cells (Ma) (B), basophils and dendritic cells. When reduction of free IgE and Fc ϵ RI occurs, this leads to a decrease in allergens processing and their presentation to T lymphocytes, causing a reduction in Th2 cells differentiation and lower expression of cytokines from this profile (IL-4, IL-5), the consequence of this is a reduction in activation of effectors cells as mast cells (Ma) and eosinophils (Eo) (C).

suggested that at least 0.2% of patients who received omalizumab experienced anaphylaxis between June 2003 and December 2006.^{10,11} A higher incidence of malignancies was observed in a group of omalizumab-treated patients 20/4127 (0.5%) compared with 5/2236 (0.2%) patients in a control group (*Xolair® (Omalizumab) for Subcutaneous Use, Genentech Inc. July 2008 2008* [http://www.xolair.com/prescribing_information.html]. Accessed 12/05/2008, 2008). The clinical data did not suggest a causal relationship between omalizumab and malignancy but the impact of longer exposure to omalizumab use in patients in higher risk for malignancy is not known. For helminth infections, cardiovascular, and cerebrovascular diseases many factors need to be evaluated before determining a causal relationship between omalizumab and these adverse events, but it has to be considered when patients and physicians choose to use this drug.

The FDA (Food and Drug Administration) approved the use of omalizumab first in patients with asthma over 12 years of age, and lately in patients of over six years; recently we reported a patient with three years with severe asthma who had an important clinical response after six months with omalizumab without adverse effects¹² and large number of publications have emerged about the use of omalizumab in patients with allergy diseases without response with standard therapy. We present a review of experimental studies and clinical efficacy of omalizumab in other diseases different to asthma.

Methods

We reviewed the literature using PUBMED, EMBASE, and LILACS for publications that used omalizumab in the treatment of patients with allergic diseases or any other diseases. Case reports and original articles published in English, Spanish or Portuguese were included. The search terms included the following key words: omalizumab, atopic dermatitis, eczema, urticaria, hymenoptera venom allergy, mastocytosis, idiopathic anaphylaxis, ocular allergy, vernal or atopic keratoconjunctivitis, rhinitis, rhinoconjunctivitis, eosinophilic gastrointestinal diseases, food allergy, and latex.

We summarised the data available according to disease, and emphasis was placed on omalizumab mechanisms of action, clinical response and side effects.

Results

Chronic urticaria and omalizumab

There are several types of urticaria with different pathophysiological mechanisms that include type I hypersensitivity and non-specific degranulation of mast cells mediated by medications, foods, infections and physical stimulation with activation of mast cells and basophiles, among other mechanisms. In 2001, urticaria was mentioned as the most frequent adverse event of omalizumab administration, because of which its use as a therapeutic tool for this disease was far from being considered; even so, the studies did not take long to come out and case reports where successful treatment of urticaria with omalizumab

was demonstrated, existing to date over 50 publications listing them. However, it is appropriate to say that most of them correspond to case reports and not controlled studies.

Omalizumab reduces FcεR1 expression on dendritic cells and basophiles and this may produce a down regulation of IgE-mediated basophile activity and in FcεR1 dependent secretion of cytokines and chemokines.¹³ Furthermore, clinical improvement is determined by an independent IgE mechanism attributed to reduction in mast cells and basophile survival, which explains why patients with low IgE levels eventually improve with omalizumab use as well.¹⁴ Other proposed mechanisms of action have been eosinophil apoptosis induction, and down regulation of cytokines such as IL-2 and 13 which interfere with proliferation of T lymphocytes. Another author reports reduction in Tumour Necrosis Factor alpha (TNF-alpha), IL-4, in B cells activation and their homing, and increase in interferon gamma (IFN-gamma) synthesis.¹⁵

Urticaria is a heterogeneous disease where clinical manifestations can be triggered by one or several stimuli but in many instances are not identified. Even so, it usually responds to a similar treatment scheme. The urticaria subtype about which more articles have been published with omalizumab has been autoimmune urticaria. Kaplan et al. reported a series of 12 urticaria patients whose autoimmune component was demonstrated through an autologous serum test, basophile histamine release test, or both. In this series, complete symptoms remission in seven patients was found after four months with omalizumab, partial improvement in four and treatment failure in just one of them.¹⁶ The clinical improvement after two years of suspended omalizumab was maintained in five patients.¹⁷ For idiopathic chronic urticaria cases, successful treatment with omalizumab has been reported as well, although its mechanism of action remains unclear.^{14,18,19} In some forms of physical urticaria, immunoglobulin E (IgE) has been hypothesized to be the critical factor in the activation of mast cells, although specific allergens, i.e. a photoallergen in solar urticaria or a cold-induced allergen in cold contact urticaria, have yet to be identified.²⁰ The presence of a more typical antigen-antibody reaction has also been investigated. Murphy et al. performed passive transfer experiments using sera from patients with cholinergic urticaria that were injected into primate skin.²¹ When monkeys were injected with acetylcholine, a skin reaction was observed in 7 of 16 monkeys' sera. This finding seemed to suggest that a transferable serum factor exists in at least some patients with cholinergic urticaria. Several authors have found clinical improvement with omalizumab use, positive results both in isolated cases reports and case series of physical urticaria from diverse aetiologies²²; solar urticaria,²³⁻²⁵ cold urticaria,²⁶ retarded pressure associated with autoimmune urticaria²⁷ and controversial results in cholinergic urticaria have been reported.²⁸⁻³⁰

With vasculitic urticaria some reports have been done as well; Callejas et al. described two female patients aged 60 and 30 years who did not achieve improvement with multiple antihistaminic agents, steroids, immunomodulators and even intravenous IgG use, and achieved total control of their symptoms after starting omalizumab treatment.³¹ One report of three patients with idiopathic angio-oedema refractory to conventional medical treatment who improved

with omalizumab points out that this monoclonal could be an alternative treatment in these cases when conventional therapy is not effective.³²

Omalizumab and atopic dermatitis

Atopic dermatitis is an inflammatory skin disease characterised by eczema and intense pruritus. Despite its high prevalence, the current knowledge of the pathophysiology is incomplete, particularly concerning the IgE role in the disease process. Owing to the important Th2 component in this disease, the therapeutic effect of free IgE blockage has been studied, reporting in most cases an important improvement even when using omalizumab as monotherapy.^{33,34} Atopic dermatitis patients usually have higher total IgE levels than asthmatic patients, and some concerns arise about what dose should be administered when 450 mg is the maximum dose recommended for asthma according to the weight and total IgE level that is usually less than 1000 KU/L. Joshua et al. gave the omalizumab maximum recommended dose to three recalcitrant atopic dermatitis patients with IgE levels over 1000 KU/L. Following a six-month treatment, patients showed a remarkable improvement of eczema, reason why they suspend corticosteroids.³⁵ Other studies have showed that atopic dermatitis patients with IgE high levels (>1000 kU/L) and low omalizumab doses can achieve some grade of control. Belloni et al. studied 11 patients to whom low omalizumab doses (150 mg) were given twice-monthly. After five months they observed significant improvement in six patients while three patients showed no significant clinical changes, and two patients showed worsening of eczema. Additionally, they found that this omalizumab dose resulted in a significant IgG increase correlated with the clinical improvement, setting forth that IgE/IgG ratio could be useful for assessing the response to omalizumab,³⁶ although the question as to whether these patients could have achieved improvement with anti-IgE higher doses remains to be answered. Since some atopic dermatitis patients do not have elevated total IgE levels it has been questioned whether omalizumab would be useful in those cases. In a descriptive study, 21 mild to severe atopic dermatitis patients were treated with omalizumab. The patients had different total IgE levels; six patients had very high levels (>700 UI/ml), 11 high levels (186–669 UI/ml) and four normal levels (<185 UI/ml). Despite IgE levels, all patients showed significant improvement after eight months for atopic dermatitis and other allergic comorbidities.³⁷ Recently, the first double-blind randomised case-control study for omalizumab use in severe atopic dermatitis patients was reported: thirteen patients were included in the active group and seven patients in the placebo group; the treatment period lasted 16 weeks and the clinical follow-up was extended to four additional weeks. Patients were allowed to use only emollients and 1% hydrocortisone aceponate. The authors observed a significant reduction of serum total free IgE levels, FcεR1 reduction in peripheral blood cells and lower IgE binding to its receptor in the omalizumab group. A higher tolerance threshold for a positive prick test was observed, assessed with different sensitising allergens concentrations as well as an atopic patch test improvement; these changes at the cellular and humoral levels were not accompanied

by a significant improvement in clinical parameters. The authors put forward that this lack of clinical response may be caused by poor omalizumab penetration inside the skin and its benefits would be primarily in reducing atopic dermatitis acute crisis rather than in chronic disease patients.³⁸ However, another possibility is that the short period of omalizumab treatment and clinical follow-up would not be enough to observe clinical improvement in atopic dermatitis. More studies are necessary to define the real impact of this therapy in atopic dermatitis.

Omalizumab hymenoptera venom allergy and associated mastocytosis

Hymenoptera venom allergy (HVA) is an IgE-dependent allergic reaction in which there has been prior insect sensitisation. The symptoms range from local manifestations in the sting site to life endangering reactions such as anaphylaxis.^{39,40} Approximately 34% of anaphylactic reactions are caused by HVA⁴¹ and between 1% and 8% of the population with anaphylaxis after hymenoptera stings have mastocytosis which is a disorder characterised by mast cell proliferation and accumulation within various organs, most commonly the skin and heart.^{39,42,43} Specific venom immunotherapy (SVI) is indicated in patients with systemic reaction and evidence of venom sensitisation.⁴⁴ In 3–12% of patients a new severe systemic reactions can occur with the immunotherapy.⁴⁵ Combined therapy with omalizumab has been used successfully to reduce the incidence or systemic allergic reactions (SAR) which can occur upon SVI.⁴⁴ Galera et al. report a case of a 33-year-old apiarist woman who presented an almost fatal SAR caused by bee sting. SVI starting dose of 20 µg was discontinued due to the presence of anaphylaxis. One month later, SVI starting schedule was changed and had to be discontinued again due to a new episode of anaphylaxis. Subcutaneous omalizumab was started six weeks previously a new cycle and every two weeks thereafter. After 12 months following treatment she was stung by a bee and only developed a local reaction.⁴⁵ The same authors performed a review of six additional cases of SVI with omalizumab finding differences between the treatment protocols, though with promising results regarding omalizumab use as a therapeutic option in patients with HVA and SAR who do not tolerate SVI alone; in two of the cases, a omalizumab single dose was enough for tolerating SVI.^{45,46} In two other case reports, one or two omalizumab doses were used prior to SVI starting dose and during the first three doses of maintenance therapy tolerating without reactions to SVI even when omalizumab was suspended.^{45,47} Omalizumab has also been used associated with SVI in systemic mastocytosis patients, although there is a lot of controversy regarding the management of these patients.³⁹ Kontou-Fili and Filis reported a 45-year-old patient with indolent systemic mastocytosis and HVA who presented an almost fatal SAR owing to SVI; one week before starting SVI he was given omalizumab at double recommended dose for his weight and total serum IgE level; he experienced no adverse effects with further tolerance to SVI at a dose of 150 µg.⁴⁸

These results suggest that omalizumab could be used in patients with hymenoptera venom allergy with or without

mastocytosis as a premedication to prevent reactions with SVI; however, is not clear for how much time it should be used.

Idiopathic anaphylaxis and mastocytosis

Anaphylaxis is a systemic reaction usually IgE-mediated but may also occur through other immunologic non-immunoglobulin-mediated mechanisms. Idiopathic anaphylaxis is an exclusion diagnosis performed after ruling out all likely causes of anaphylaxis in each patient. In the United States, the estimated prevalence of idiopathic anaphylaxis is 20,000–40,000 cases per year, being potentially fatal.⁴⁹ Even though anaphylaxis is one of omalizumab's potential adverse effects, currently there are some reports on omalizumab use as a therapy in idiopathic anaphylaxis patients.¹⁰ Jones et al. reported in 2008 the case of one recurrent anaphylaxis patient with no allergen or associated disease who started omalizumab because of high IgE levels (1821 IU/ml). The patient was followed up for one year from omalizumab therapy start and he did not experience new anaphylaxis episodes thereafter.⁵⁰ Warrier and Casele presented the case of a patient with more than three anaphylaxis episodes per month; due to the frequency of the episodes and the secondary effects result of steroids chronic use, omalizumab therapy was started with no new anaphylaxis episodes presented by the patients after one-year follow-up.⁵¹

Despite the fact that in idiopathic anaphylaxis no allergen is identified, IgE is known to play an important role in its pathogenesis, although this is not the only mechanism of the disease; the presence of some autoimmune mechanisms mediating FcεR1 activation in the mast cells membrane inducing its mediators release has been demonstrated.⁵² Since 2009, the US National Institute of Allergy and Infectious Diseases (NIAID) has been carrying out a project with the aim of studying the effect of omalizumab on idiopathic anaphylaxis patients through a controlled double-blind study. This study is also intended to identify idiopathic anaphylaxis patients with undiagnosed mastocytosis and the cellular and molecular effects omalizumab may have on mast cells and basophiles (*A Randomized, Double-Blind, Placebo-Controlled Study of Omalizumab for Idiopathic Anaphylaxis* <http://clinicaltrials.gov> NCT00890162).

In mastocytosis patients, activation of mast cells seems to be caused more by unspecific stimuli or cell intrinsic abnormalities than by specific sensitisation.⁵³ The clinical manifestation of mastocytosis could be only in skin (pigmentous urticaria) or systemic (anaphylaxis). Carter et al. assessed two pigmentous urticaria patients with more than three anaphylaxis episodes annually with poor response to systemic steroids. Both patients had allergic antecedents, and in each episode of anaphylaxis known allergen sources such as foods, drugs, physical activities or insect sting was ruled. Patients were given omalizumab and although they showed no changes in serum tryptase levels both stopped presenting anaphylaxis episodes and had a better control of pigmentous urticaria, one of them from the first omalizumab dose and the other one from the fifth dose.⁵⁴ Douglass et al. observed similar results in a systemic mastocytosis patient with no antecedent of atopy who experienced around four anaphylaxis episodes per year. He started omalizumab and

no anaphylactic episodes after one-year follow-up were reported.⁵⁵ Pitt et al. assessed the effect of omalizumab in a patient with lesions suggesting pigmentous urticaria and high levels of tryptase who had experienced five anaphylaxis episodes within the last year. After omalizumab was started the patient presented no new episodes.⁵⁶ These results would be showing that the effect of omalizumab can be useful in both atopic and non-atopic patients.

Controlled studies allowing the assurance of a cause effect relationship between clinical improve with omalizumab in mastocytosis and anaphylaxis are needed. If the effect of omalizumab in mastocytosis and anaphylaxis is because of IgE blockage or due to other mechanisms is not clear.

Rhinitis, ocular allergy and omalizumab

Ocular and nasal allergic symptoms usually appear together. Seasonal and perennial conjunctivitis and allergic rhinitis are mediated by IgE, Th2 type cytokines, and mast cells. Vernal and atopic keratoconjunctivitis are mediated by Th1 and Th2 inflammatory profile, with massive involvement of T cells, macrophages, neutrophils and eosinophils.⁵⁷ Most studies evaluated the effect of omalizumab in rhinitis and ocular allergy as a secondary outcome but there are some studies which focus on this point. Okubo et al. observed a significant improvement in a group of seasonal rhinoconjunctivitis patients following a four-month period of treatment before spring when the concentration of pollen is high.⁵⁸ After one year, a re-treatment was provided with omalizumab in 34 patients with a better response and control of nasal and ocular symptoms being found.⁵⁹ Nagakura et al. observed in a controlled study performed in a group of patients treated with omalizumab, lesser symptoms compared with a group treated with suplastat tosilate.⁶⁰ Casale et al. assessed the efficacy and safety of omalizumab for prophylaxis of symptoms in patients with seasonal allergic rhinitis in a randomised control trial with over 500 patients. They observed that nasal symptom severity scores and rescue antihistamine use were significantly lower in patients with omalizumab. The omalizumab group have also decreased serum free IgE levels.⁶¹ Nayak et al. assessed the safety and tolerability of retreatment with omalizumab in 287 patients previously treated with this agent and they found that there were no severe adverse events related to omalizumab treatment and no anti-omalizumab antibodies were detected in any patients.⁶²

Additionally to conjunctivitis typical symptoms, atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) produce conjunctival and corneal damage which can lead to blindness. The management of these diseases used to be complicated and their pathophysiology is not totally clear. Few studies have been performed studying the effect of omalizumab in these patients, all of them being case reports. Williams and Sheppard described seven keratoconjunctivitis patients: three VKC and four AKC patients, who also had other allergic diseases such as asthma, atopic dermatitis and rhinitis. Six of the patients had a significant improvement of symptoms while one of VKC patients showed no noteworthy changes.⁶³ Recently, we reported a VKC 15-year-old patient who had not improved with steroids and

other topical immunosuppressive drugs following several years of treatment and who required bilateral corneal transplant. Since he also had uncontrolled asthma we started omalizumab therapy obtaining respiratory symptoms control and significant ocular improvement after three months.⁶⁴ One year after starting treatment the patient presented a remarkable reduction of tarsal papillae and excellent control of pruritus. VKC is a disease with a Th1 and Th2 profile and the action of omalizumab is maybe through the immunomodulator effect of Th2 response; however, more studies are necessary to support the use of omalizumab in keratoconjunctivitis.

Omalizumab and eosinophilic gastrointestinal diseases

Eosinophilic gastrointestinal disorders are characterised by eosinophilic infiltration and inflammation in one or more segments of the gastrointestinal tract in the absence of previously identified causes of eosinophilia. These disorders include eosinophilic oesophagitis (EO), eosinophilic gastroenteritis (GE), eosinophilic enteritis and eosinophilic colitis. In the past, EO was considered as a rare condition, but now is recognised as a nosological entity in children and adults; it can occur alone or as part of other eosinophilic gastrointestinal diseases.⁶⁵

The causes of EO are poorly understood yet allergy has been markedly implicated. Sensitisation frequency in patients with these alterations has been estimated at 25–75%.⁶⁶ Most of them have evidence of hypersensitivity to foods and/or aeroallergens defined by skin tests (prick test), specific IgE measurement or both, although only a minority have food anaphylaxis history, indicating different mechanisms and not only the classic type I hypersensitivity reaction.⁶⁷ The IgE role in gastrointestinal eosinophilic diseases pathogenesis is clear although this is not an exclusively type I disorder.⁶⁸ In a food antigen-challenged mice model, similar responses to human gastrointestinal disease have been observed, such as specific IgE and IgG1 antibodies, intestinal eosinophilic infiltrate widely located in the lamina propria mainly at the small bowel level yet also in the oesophagus, stomach and Peyer's patches, and clinical manifestations such as diarrhoea, gastromegaly, motility disorders and cachexia.⁶⁹

Medical literature reports on omalizumab use in gastrointestinal tract diseases are scarce. Foroughi et al. performed a study assessing omalizumab efficacy in nine adult patients aged between 30 and 60 years receiving a 375 mg dose every 15 days for 16 weeks. A 35–45% reduction in peripheral blood eosinophil count and 60–70% reduction in tissue eosinophils was found in the gastric antrum and duodenum contrasting with a slight increase in oesophageal eosinophils with no symptoms increase. Reduction in IgE FcεRI expression in basophils (75%), and in dendritic cells (81%) was observed. Although it was not the study objective, patients reported a 60–70% reduction in symptom score. Wheal and erythematous in skin prick test decreased 78 and 82%, respectively and higher tolerance to allergens for triggering basophile activation was found.^{70,71}

Currently, in Virginia State, USA, Alpan and Kaushal are performing an interventional study in eosinophilic

oesophagitis patients aged 12–76 years who were diagnosed through biopsy; the patients receive omalizumab every two to four weeks according to the required dose per weight and IgE levels (Title: *"Identifying Responders to Xolair (Omalizumab) Using Eosinophilic Esophagitis as a Disease Model."* ClinicalTrials.gov identification: NCT01040598).

Another ongoing interventional, double-blind, randomised, placebo-controlled study by Fang et al., from the University of Utah, is aimed at determining the efficacy of omalizumab given every four weeks for 16 weeks in eosinophilic oesophagitis patients aged 12 and 60 years (Title: *"A Pilot Study of the Treatment of Eosinophilic Esophagitis With Omalizumab."* ClinicalTrials.gov identification: NCT00123630).

Omalizumab and food allergy

Food allergy is a Th2 disease affecting principally the gastrointestinal tract, usually after sensitisation with food allergens. Currently, there are few published papers assessing the impact of omalizumab in the management of food allergy. Furthermore, since a lot of people have symptoms following food intake owing to non-allergic causes, the diagnosis and management of these patients can be challenging for the clinician. Oral challenge test along with a demonstrated sensitisation to a dietary allergen are the most useful tools for the diagnosis, although, due to the risk of anaphylactic reactions following food intake, challenge tests are only given in selected cases. In case reports omalizumab use has proved to be useful in patients with gastrointestinal symptoms following food intake^{72,73}; however, in most occasions patients start omalizumab due to other allergic disease and the component of the alimentary allergy is not described in detail.⁷⁴ In 2010 Rafi et al. assessed the efficacy of omalizumab in 22 asthma patients with antecedents of skin, respiratory, gastrointestinal or anaphylactic symptoms following the food intake. All patients were sensitised to one or more foods with a clinically suspected allergic reaction. Between associated foods there were fruits, vegetables, milk, meats, fish, eggs, shellfish or dried fruits. The age range was 4–66 years and mean IgE was 1120.74 IU/ml (range 30–5200 UI/ml). All patients presented significant improvement consisting in food tolerance when facing new exposures. Most patients started to notice improvement following a three-month treatment with omalizumab; however, the range for achieving a good control ranged from three months to 18 months. Regarding food-associated pathologies, eight patients noticed atopic dermatitis improvement, 13 noticed asthma reduction, three noticed urticaria reduction, six noticed rhino-sinusitis reduction and nine patients either achieved angio-oedema reduction or tolerated food with no presence of anaphylaxis or severe skin reaction.⁷⁵ Even though the patient-reported improvement was remarkable it is necessary to be careful when analysing the results because no oral challenge test was done to the patients prior to the start of omalizumab, and neither the objective assessment parameters were reported nor the effect of other concomitant therapies was evaluated through a control group. This type of inconveniences is found in most of the studies assessing the relationship between omalizumab use in other diseases different to asthma.

One study suggested that anti-IgE (Hu-901) might be effective for the treatment of peanut allergy.⁷⁶ Hu-901 was not selected for further clinical developments, but a randomised controlled trial was intended to assess the efficacy of omalizumab, in patients with peanut allergy.⁷⁷ The study was designed to compare changes in peanut tolerability thresholds in subjects with proven peanut allergy who were treated with either omalizumab or placebo. Although the study intended to randomise 150 subjects, it was stopped because of the severity of two anaphylactic reactions that occurred during the qualifying oral food challenges (OFCs) before the administration of the study drug. Consequently, only 14 subjects reached the study's primary endpoint before the discontinuation of the trial. Despite the small number of subjects enrolled, some favourable trends in post-therapy peanut challenge thresholds were noted.

These limited data are consistent with findings with HU-9015 and suggest that Anti-IgE therapy may increase the tolerability to peanut in patients with peanut allergy.

Omalizumab and latex allergy

Natural rubber latex comes from *Hevea brasiliensis* rubber tree and is found in many common products such as gloves, balloons, preservatives, adhesive bandages, and nursing bottles teats among other things.^{78,79} The prevalence of latex allergy in the general population is 1%. In healthcare workers, sensitisation rates show a high increase in comparison with the general population (5–15%).⁸⁰ The latex allergy clinical spectrum and severity is ample with many reports of rhino-conjunctivitis, asthma, urticaria, food allergy and anaphylaxis.⁷⁹

A randomised, double-blind, placebo controlled study was carried out by Leynadier et al.⁸¹ with the aim of determining whether anti-IgE therapy benefits can be translated to latex allergic patients. Eighteen healthcare workers were chosen who were latex-sensitised and had experienced labour-related latex allergy symptoms. Half the patients were treated with placebo and the other half with omalizumab at a dose of 150–750 mg/month for 16 weeks. The efficacy was assessed through conjunctival challenge tests following 8- and 16-week treatment along with skin reactivity test at three latex dilutions. Among the total patients, two from the omalizumab group discontinued the therapy for unspecified reasons, and in the remaining patients, reduction in symptoms score was found following the conjunctival challenge test in four. Subsequently, all 16 subjects were given omalizumab for 16 additional weeks and eight of nine who had received baseline placebo were able to tolerate the conjunctival challenge tests. At the end of the study, all patients treated with omalizumab for 32 weeks showed a reduction in the skin test indicating a better control of the IgE-mediated response.

Other potential uses of omalizumab in no classical IgE diseases

Ménière's disease consists of an inner ear disorder causing vertigo, tinnitus and fluctuant loss of the auditory capability. Frank S presented the case of a patient who had Ménière and mastocytosis and attained remission of the symptoms

caused by both pathologies following omalizumab use.⁸² The aetiology of Ménière's disease is unknown but probably there is an IgE-mediated mechanism since control patients with this disease plus an allergic disorder exhibit improvement in both pathologies with treatment intended for the allergic disease.⁸³

Churg-Strauss Syndrome (CSS) is a systemic necrotising vasculitis affecting medium and large diameter vessels, characterised by asthma, eosinophilia and granulomatous inflammation in various tissues where there is intervention of both Th2 profile and autoimmune mechanisms. Several case reports have shown a temporal relationship between the development of CSS and omalizumab use; this is why on some occasions it is considered as a potential adverse effect as a result of this drug use.^{84–86} However, some authors consider that in those case reports showing a relationship between omalizumab and the development of CSS, chronic use of steroids, either oral or inhaled, could have been masking the CSS, and once the steroid dose was reduced due to better asthma control with omalizumab, the CSS became evident.

Giavina-Bianchi et al. reported one case of a CSS patient who was treated with omalizumab for three months for asthma control with excellent results on the respiratory function and a significant reduction in eosinophilia at three months⁸⁷; after one year, the patient was not receiving steroids and continued receiving omalizumab with no occurrence of relapses.⁸⁸ Pabst et al. reported two cases of frustrated-form-CSS patients who presented with an acute event of systemic involvement with proteinuria and haemodynamic instability owing to lack of response on steroids, cyclosporine and cyclophosphamide; it was decided to start omalizumab therapy. Despite one of the patients having very low IgE levels, at the second dose both patients were stable and have had a sustained reduction of eosinophilia and after one year they used omalizumab as a single immunomodulator drug.⁸⁹ These reports point out that omalizumab is a useful and safe management and rescue alternative in CSS patients maybe because of its ability to regulate the increased Th2 response present in this disease; however, there is not enough evidence to recommend omalizumab in CSS patients and the risk has to be evaluated.

Hyper IgE syndrome is a rare primary idiopathic immunodeficiency characterised by high IgE levels, skin abscesses and pneumonia and the aetiology are genetic polymorphisms in different chromosomes and is not considered an allergic disease. Chularojanamontri et al. reported a hyper IgE syndrome patient case who was successfully treated with omalizumab with a significant reduction of skin abscesses recurrence⁹⁰; similar results were found in another hyper IgE syndrome patient.⁹¹ Yet, since patients have a higher risk of recurrent infections with omalizumab and omalizumab in some way is an immunosuppressor its usefulness could be limited.

Bronchopulmonary aspergillosis is a disease characterised by progressive pulmonary changes secondary to an allergic reaction to *Aspergillus fumigatus*.⁹² Several case reports have shown that omalizumab use significantly reduces total free IgE levels and *Aspergillus fumigatus* specific IgE in bronchopulmonary aspergillosis patients.^{93–99} However, the clinical impact that omalizumab can have on

this pathology is not clear; most reported cases are patients on omalizumab along with oral steroids and thus its effect cannot be clearly determined.

Conclusions

Tremendous progress has been made in the past few decades in translating basic findings about the immune system into new therapies that have had a substantial effect on human health. Patients without response to conventional therapy have to deal with symptoms and in some cases, with the risk of deterioration and death. In those cases, alternative therapies are needed and healthcare personal have to choose between options with little or no clinical and experimental evidence. The better understanding of the role of immunoglobulin E in the physiopathology of some diseases has shown that anti-IgE treatment could be a therapeutic option. In the last 10 years, many articles on omalizumab therapy in the treatment of other IgE-mediated diseases have shown important clinical benefit. Since most of this information comes from case reports and uncontrolled studies, it is necessary to be careful with the interpretation of the results. These cases reports and a few controlled trials show that omalizumab could be an option and encourages to conducting investigational studies to evaluate the real effect of omalizumab compared with others therapeutic alternatives. More articles have evaluated the efficacy of this treatment but the safety has not been specifically stated. Studies focusing on this important point are required. At the moment, omalizumab is only approved for asthma and most of the literature evaluates the mechanisms of action in this disease. We cannot extrapolate these results to other IgE diseases without first carrying out laboratory studies to evaluate the effect under experimental conditions that mimic other IgE-mediated diseases and also in randomised control trials, and after that, the efficacy and safety of this biological therapy can be estimated in each IgE disease. These investigations are going to happen in coming years: some international trials and multicentre studies are taking place and they could serve as the opening for studies in other IgE-mediated diseases unexplored at the moment. We hope with optimism that the results of these investigations will help us to understand the real role of omalizumab beyond asthma and also to incorporate a new therapeutic alternative in some of these IgE diseases. Finally there is the economical issue. Treatment with omalizumab is expensive and studies of cost-benefit analysis are scarce in asthma and there are none for other diseases. It can be argued cogently that success in exploring the effect of omalizumab in other diseases will lead to new methods for treating these diseases and preventing complications, with a decrease in overall healthcare costs in the long term.

Conflict of interest

The authors have no conflict of interest.

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