

Off-Label Uses of Omalizumab

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Abstract The off-label use of medicines is a common and extensive clinical practice. Omalizumab has been licensed for use in severe allergic asthma and chronic urticaria. Omalizumab dosing was based on body weight and baseline serum IgE concentration. All patients are required to have a baseline IgE between 30 and 700 IU/ml and body weight not more than 150 kg. The use of off-label drugs may lead to several problems including adverse effects and an increased risk/benefit balance. In this article, there are summarized off-label uses of omalizumab in the last recent years in diseases in which IgE maybe or certainly has a corner role such as allergic rhinitis, allergic bronchopulmonary aspergillosis, anaphylaxis, keratoconjunctivitis, food allergy, drug allergy, urticaria, angioedema, non-atopic asthma, atopic dermatitis, nasal polyps, Churg-Strauss syndrome, eosinophilic otitis media, chronic rhinosinusitis, bullous pemphigoid, contact dermatitis, and others. Use in pregnancy asthmatic women and pre-co-administration with specific immunotherapy will also be revised.

Keywords Off-label · Omalizumab · Anti-IgE · Xolair · Intrinsic asthma · Atopic dermatitis · ABPA

Introduction

Off-label medicine use includes the treatment with a medicine for an indication, a route of administration, or a patient group that is not permitted in the summary product characteristics [1]. The term does not imply improper nor illegal use. The off-label use of medicines is a common and extensive clinical practice. Radley et al., using data from a nationally representative survey of office-based physicians, found that about 21 % of all estimated uses for normally prescribed medications were off-label, and that 15 % of them lacked scientific evidence of healing efficacy [2]. However, the use of medicines outside the approved clinical indications may lead to several problems: lack of effective pharmacovigilance with increased risk for the patient, rise in the individual physician's civil and criminal responsibility, and, potentially, increased cost of treating patients. Additionally, off-label use of medicines can cause adverse effects and the risk may be more important than the potential benefits. Furthermore, ethical and legal problems associated to the off-label use of these medications have also increased [3].

Omalizumab (Xolair[®], Novartis, Basel, Switzerland) is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to free and membrane-bound immunoglobulin E (IgE) antibodies. The Cε3 region of the Fc fragment of IgE binds very selectively to a particular component of the α-chain of the tetrameric FcεR1 (α1β1γ2) [4]. Omalizumab binds to free IgE in the circulation and not to receptor-bound IgE. So, blocking IgE, specifically, in the Cε3 region produces avoidance of crosslinking of IgE bound to its high-affinity receptor. Omalizumab has been licensed for use in severe allergic asthma and chronic urticaria. The urticaria dosage is not dependent on serum IgE levels and response is seen very often after only 12 h [5]. Use of omalizumab in chronic urticaria was off-label at the beginning of its commercial use.

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The mechanism(s) of omalizumab in reducing total free IgE probably leads to the observed beneficial effects without being dependent on specific IgE. Omalizumab complexes with seric-free IgE results in down-regulation of expression of the high-affinity IgE receptor on mast cells and basophils and consequently a reduction in cellular activation and mediator release [6]. Omalizumab in severe allergic asthma has a powerful effect on asthma exacerbations, patient-related and quality of life measures, but less effect on measures of lung function [7]. Currently, you can search on ClinicalTrials.gov, and you can notice that more than 30 open clinical trials with omalizumab of which, approximately, 50 % are for conditions other than asthma. In addition to asthma, omalizumab has been investigated in perennial and seasonal allergic rhinitis, peanut allergy, latex allergy, atopic dermatitis, idiopathic anaphylaxis, mastocytosis, eosinophilic gastroenteritis, and nasal polyposis [8].

In the last years, the use of several off-label has increased. Recently, a multicentric prospective cohort study of 226 patients treated with off-label medicines was carried out in five tertiary hospitals from May 2011 to May 2012 [9]. Omalizumab was used in 6 % of patients. The clinical responses to off-label use of drugs were classified as complete response (CR), partial response (PR), stabilization (S), and no response (NR) taking into account different parameters of efficacy. In 164 (72.6 %) patients, a clinical response was observed (82 [36.3 %] with a PR, 71 [31.4 %] with a CR, and 11 [4.9 %] with a S); in 59 patients (26.1 %), a NR was documented and in 3 (1.3 %), it was unknown. Author concluded “Although the clinical evidence of off-label medicines was often low, a high percentage of some clinical responses in patients with previous multiple treatment failures was observed. However, this was at the expenses of adverse effects (some of them severe) and a high cost.”

In this article, we review off-label uses of omalizumab in the last recent years in diseases in which IgE maybe or certainly has a central role such as allergic rhinitis (AR), allergic bronchopulmonary aspergillosis (ABPA), anaphylaxis, keratoconjunctivitis, food allergy, urticaria, angioedema, non-atopic asthma, atopic dermatitis (AD), nasal polyps, Kimura's disease, Churg-Strauss syndrome (CSS), eosinophilic otitis media (EOM), chronic rhinosinusitis, bullous pemphigoid (BP), contact dermatitis, and others. Use in pregnancy asthmatic women and before administration of specific immunotherapy will also be revised.

Respiratory Diseases

Currently, the administration of omalizumab in pregnancy women is not recommended. The first report in Japan of a woman who received omalizumab during pregnancy and delivery was in 2009 [10]. However, after an asthma

exacerbation, the patient decided to suspend omalizumab therapy after taking the drug seven times, as she was not feeling any benefit from therapy. Authors considered that omalizumab may be safe to use in pregnant women. In 2014, in another two cases, treatment with omalizumab did not affect pregnancies and newborns [11]. EXPECT is a prospective and observational study that evaluates maternal, pregnancy, and infant outcomes after exposure to ≥ 1 dose of omalizumab, including incidence of congenital anomalies [12]. The authors concluded “no apparent increased birth prevalence of major anomalies or patterns of major anomalies has been observed.”

Omalizumab dosing was based on body weight and baseline serum IgE concentration. All patients are required to have a baseline IgE between 30 and 700 IU/ml and body weight not more than 150 kg according to summary of product characteristics. In the first clinical trials, the patients were treated according to a table in order to receive at least 0.016 mg/kg/UI (IgE/ml) of omalizumab. Apparently, omalizumab does not offer any benefit and should not be used in patients with IgE levels < 30 IU/ml. However, many atopic patients with severe allergic problems have such low levels but an important percentage have also higher total IgE levels than 700 UI/ml. Among sera sent to the Allergy Laboratory at Karolinska University Hospital, with suspected cat or mite allergy and with a total IgE level lower than 30 kU/l, 14.5 % were positive to cat and 8.3 % to mite [13]. In 2006, two patients with low total IgE and a large disease-relevant IgE fraction were effectively treated with omalizumab. However, the dosage had to be increased to fourfold that recommended for patients with their IgE body pool [14]. On the other hand, to evaluate the response of asthmatic patients treated with omalizumab with IgE levels greater than 700 kU/ml, 26 patients with a total IgE level greater than 700 kU/ml were compared to patients with an IgE of 30 to 700 kU/ml [15]. Authors showed no statistical differences in number of emergency department (ED) visits, asthma control test (ACT), and reducing the need for systemic corticosteroids in both groups of patients. Patients with IgE levels above 700 kU/ml received at least 0.016 mg/kg of IgE every 4-week period, with a mean of 0.007 mg/kg/month per unit of total IgE mg/month.

Intrinsic Asthma

When a specific allergen sensitization is not found in an asthmatic patient, neither excludes an atopic mechanism nor the role that IgE may play in asthma. Omalizumab should be tried in patients with uncontrolled severe asthma, although there is a lack of IgE-specific sensitization [16]. There are now published studies including an important number of patients with uncontrolled intrinsic asthma showing a reduction in exacerbation rates and an improvement in symptom scores during omalizumab treatment. In 2013, De Llano et al., using data

from a multicenter registry of severe asthma, analyzed 29 patients with intrinsic asthma treated with anti-IgE and compared them with 266 omalizumab-treated severe allergic asthmatics [17]. Omalizumab treatment over 2 years significantly increased asthma control in these patients, and was associated with a trend to reduced exacerbation rates and improved lung function. That year, Garcia et al. investigated whether omalizumab has biologic and clinical effects in patients with uncontrolled intrinsic asthma [18]. Compared with placebo, omalizumab resulted in a statistically significant reduction in FcRI expression on basophils and produced an overall increase in FEV1 compared with baseline. The same year, Domingo et al. conducted a study to evaluate the effectiveness and tolerance of this drug in non-allergic seven adult asthma patients [19]. Authors concluded that there is no sufficient support to systematically prescribe omalizumab in non-allergic asthma patients.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) could be a complication of cystic fibrosis (CF). The diagnosis of ABPA in cystic fibrosis is difficult because many of the diagnostic criteria overlap with common manifestations of cystic fibrosis. The 2001, Bethesda-Maryland consensus established a minimal diagnostic criteria for the diagnosis of ABPA in CF [20]:

1. Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another etiology.
2. Total serum IgE concentration of 1500 IU/ml.
3. Immediate cutaneous reactivity to *Aspergillus fumigatus*.
4. One of the following: (a) precipitins to *A. fumigatus* or in vitro demonstration of IgG antibody to *A. fumigatus*; or (b) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

The diagnosis of ABPA without CF is based on clinical and immunologic criteria. The minimal criteria required for the diagnosis of ABPA are (a) asthma, (b) immediate positivity to *Aspergillus* skin test, (c) total serum IgE ≥ 1000 IU/ml, (d) elevated *Aspergillus*-specific IgE and IgG antibodies, and (e) chest radiographic infiltrates. Additional criteria may include peripheral blood eosinophilia, *Aspergillus* serum precipitating antibodies, central bronchiectasis, and *Aspergillus* in mucus plugged [21]. ABPA affects approximately 1–2 % of asthmatic patients [22] and 7–9 % of CF patients [23].

Omalizumab, as treatment of allergic bronchopulmonary aspergillosis in a patient diagnosed at birth with mild-to-moderate cystic fibrosis for a prolonged period, can resolve

clinical symptoms of asthma as published by Zicari [24]. Tanou et al. published in 2014 a complete review including 8 case reports in which 13 children with CF and ABPA received omalizumab resulting in improved FEV1, fewer respiratory symptoms, and decreased corticosteroid use [25]. The first case report published was in 2007 [26]. However, the experience cases reported lacked a comparison, placebo-treated group. Lehmann et al. published their experience with omalizumab in six patients with CF and ABPA, and all patients showed an improvement, but omalizumab therapy was less effective in patients with progressed lung disease and long-term ABPA [27]. Finally, Jat et al. published a Cochrane review about anti-IgE therapy for ABPA in CF patients and authors concluded that there is lack of evidence for the efficacy of omalizumab therapy in patients with CF and ABPA [28]. There is a need for large prospective randomized controlled trials. In fact, only one trial enrolling 14 patients was eligible for inclusion in the review.

Several case series has been reported of successful therapy with omalizumab in ABPA patients without CF [29–33]. Anti-IgE therapy produced steroid-sparing effect, reduced systemic inflammatory markers, and resulted in improvement in ACT scores in patients with ABPA.

In 2009, Gonzalez de Olano et al. reported a case of allergic bronchopulmonary candidiasis successfully treated with omalizumab [34]. However, not always omalizumab has been useful in controlling asthma symptoms in adult ABPA patients [35].

Nasal Disorders

The management of AR is based on four cornerstones: education of the patient, allergen avoidance measures, symptomatic treatment, and allergen immunotherapy [36]. Fortunately, the future will bring new therapies including combination therapy with intranasal antihistamines and corticosteroids, the anti-IgE antibody omalizumab, histamine H3 and H4 receptor antagonists, cytokine inhibitors, and toll-like receptors targeted treatment [37]. However, the high cost of omalizumab exclude its wide use for allergic rhinitis, and it is not FDA licensed for this indication [38]. In Europe, drugs which already received European marketing authorization will in general be “off-label,” drugs without such a permission will be “unlicensed,” and the employment of drugs which are “contraindicated” will be considered “off-label” [39]. Years ago, in 2002, a randomized, double-blinded trial to assess the efficacy and safety of omalizumab or placebo, in 221 subjects with seasonal allergic rhinitis in both a birch pollen season and a grass pollen season during two consecutive pollen seasons [40]. Each subject was started on SIT-birch or SIT-grass, and anti-IgE or placebo was started before and maintained during the anticipated pollen seasons. Combination therapy (SIT plus omalizumab) reduced symptom load over the two pollen

seasons by 48 % ($p < 0.001$) over SIT alone. This combination might be a novel strategy for the management of allergic rhinitis, particularly for polysensitized patients. In another study, omalizumab was administered with specific immunotherapy, and it significantly reduced the allergic symptoms in patients with seasonal allergic rhinoconjunctivitis and asthma in contrast with those who received only immunotherapy [41]. Another two randomized, double-blind study was conducted in Japan to investigate the safety and efficacy of omalizumab in the treatment of patients with Japanese cedar pollen-induced seasonal AR compared to placebo [42]. Omalizumab was more effective and safe than placebo. The same authors observed that re-treatment with omalizumab previously to the next pollen season was effective and well tolerated, with daily nasal as well as ocular symptom medication scores comparable with those in the omalizumab group in the first year study [43].

But, omalizumab have been used in another type of rhinitis and nasal disorders. Chronic rhinosinusitis (CRS), a subtype of chronic rhinosinusitis with nasal polyps (NP), is a difficult comorbidity of severe asthma. In 2007, eight patients were randomized in placebo group and active group (treated with omalizumab) after endoscopic sinus surgery [44]. Authors concluded that the treatment with omalizumab in the postpolypectomy management of atopic asthmatic individuals may reduce the severity of NP recurrence. Later, more cases reported showed efficacy of omalizumab in chronic sinusitis and NP [45, 46]. In 2011, Vennera et al. followed NP in 19 patients who were treated with omalizumab for severe asthma and who also had CRS with NP [47]. Omalizumab was effective in improving, or at least stabilizing, the natural course of CRS with NP in patients treated for refractory severe asthma. Same results were observed in the study of Tajiri et al. in 2013. Omalizumab improved nasal symptoms and sinus CT scores, and controlled asthma in CRS patients with severe asthma [48]. Omalizumab is also effective in allergic and non-allergic patients with NP and asthma in a randomized, double-blind, placebo-controlled study [49]. However, not all studies demonstrated clinical benefit of medical management. Pinto et al. performed a randomized, double-blind, placebo-controlled clinical trial in subjects with chronic rhinosinusitis who were treated with omalizumab [50]. Patients from active group showed improvement in the Sino-Nasal Outcome Test (SNOT-20) at 3, 5, and 6 months compared to baseline with no significant changes in the control group. The authors did not detect any differences in quality of life, symptoms, cellular inflammation, nasal airflow, and olfactory testing. The only evidence for the potential efficacy of omalizumab in NP from the studies revised suggests

that, when NP and asthma coexist, the anti-IgE may have therapeutic value on NP.

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is an anti-neutrophil cytoplasmic antibody (ANCA) associated systemic necrotizing eosinophil vasculitis, affecting small- and medium-sized vessels. Almost all patients have severe and/or difficult-to-control asthma. According to the American College of Rheumatology, four of six criteria lead to a diagnosis of CSS. These criteria are asthma, eosinophilia ($>10\%$), paranasal sinusitis, pulmonary infiltrates, histological proof of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy [51]. A link between omalizumab and CSS has been hypothesized, although it is poorly understood. Two mechanisms are possible. One is that omalizumab plays a direct causal effect in the development of CSS, the less feasible. And the second, the reduction of corticosteroids, allowed by omalizumab treatment, can unmask CSS which earlier is manifested only by asthma, as a partial expression of CSS [52], what has been termed *formes frustes* of Churg-Strauss [53]. Several case reports have been published about the association between treatment with omalizumab and CSS [54–58]. The majority of authors concluded that the emergence of CSS could be related to the reduction or withdrawal of systemic corticosteroids (the treatment of choice in this type of vasculitis) rather than to the activation of disease by anti-IgE therapy. However, Puechal et al. reported a case of CSS in a patient not receiving oral corticosteroids previously to anti-IgE therapy. However, this patient had had a previous episode of giant-cell arteritis. Omalizumab has showed effectiveness not only in adults. The first pediatric patient suffering from CSS successfully managed with adjuvant anti-IgE therapy resulting in the control of respiratory as well as gastrointestinal symptoms was reported in 2014 [59]. Therefore, before starting a patient on treatment with omalizumab, it must be revised if the patient meets CSS criteria. Anyway, in cases of confirmed or strongly suspected CSS, treatment with omalizumab would not be contraindicated necessarily [60, 61].

Eosinophilic Pneumonia

Two cases of chronic eosinophilic pneumonia have been reported who responded successfully to omalizumab [62, 63].

Occupational Asthma

Barnig et al. reported a case of severe asthma exacerbation after inhaling vapors of roasting chicken [64]. The patient was treated with omalizumab at a dose of 300 mg/month. After the second injection, she no longer experienced

symptoms upon exposure to the vapors of roasting chicken. In another case reported, a baker with occupational asthma (OA) did not tolerate specific immunotherapy using a long-acting depot extract of wheat flour (Bial Aristegui, Bilbao, Spain) and then, omalizumab therapy was initiated. Once treatment with omalizumab was initiated, the patient's clinical condition improved considerably in AQLQ scores, reduction in the use of systemic corticosteroids, and fewer ED visits [65]. But the first baker's occupational asthma case treated with success omalizumab was published in 2008 [66]. Authors directly treated the patient with omalizumab without previous immunotherapy attempt. In 2013, ten patients with severe uncontrolled OA were treated with omalizumab [67]. During treatment, nine patients have fewer asthma exacerbations and used less oral or inhaled corticosteroids. Seven patients were able to continue working at the same workplace as before treatment. The cost effectiveness of omalizumab has been demonstrated in patients with severe persistent allergic asthma [68]. In the cases reported, the treatments were cost effectiveness, although they must be carried out throughout the entire working life of the patients.

Angioedema of the Larynx

Ozturk and Kocaturk reported a 47-year-old male patient with severe idiopathic recurrent angioedema controlled by corticosteroid [69]. Once omalizumab treatment was initiated, he had no further attacks but after 3 months of stopping omalizumab therapy, he had two mild episodes that resolved with antihistamines.

Skin Diseases

Atopic dermatitis (AD) is one of the most frequent chronic inflammatory skin disorders. A considerable percentage of children with AD are at risk of developing allergic rhinitis and/or asthma [70]. Acute AD skin lesions is characterized by intensely pruritic, erythematous papules associated with epidermal intercellular edema as well as increased Langerhans cells, inflammatory dendritic epidermal cells, macrophages, eosinophils, and CD4-activated Th2 cells [71]. Chronic AD is characterized by thickened skin with accentuated markings (lichenification) and fibrotic papules. Conventional treatment includes emollients, antihistamine agents, corticosteroids, and calcineurin inhibitors, all of which can achieve adequate control in patients with mild-to-moderate AD; however, clinical manifestations and lesions are difficult to control in patients with severe AD [72].

Administration of omalizumab to treat AD is subject of debate. A number of studies have been published on the effectiveness of omalizumab in atopic dermatitis, and the results are controversial. In 2005, Krathen and Hsu observed no

response to omalizumab in three patients with severe AD when administered for 4 months [73]. However, same year, Lane et al. reported three patients with severe, recalcitrant atopic dermatitis successfully treated with omalizumab [74]. In 2006, Vigo et al. reported a significant improvement in the symptoms of all 7 AD patients treated who received omalizumab for their persistent asthma [75]. In 2007, Belloni et al. showed favorable response only in 6 of 11 patients [76]. Forman and Garrett reported a case of a 41-year-old black man who presented with chronic severe AD that only responded to oral corticosteroids. He responded to a 12-week course of omalizumab [77]. In 2008, Incorvaia et al. published another case report of a 39-year-old woman with severe asthma and severe AD, both resistant to conventional drug treatment who was treated with omalizumab and after 5 months was completely cured [78]. The same year, a pilot study treated with omalizumab 21 AD patients. All of them showed clinical and statistically significant improvement of their atopic dermatitis [79]. In 2010, Caruso et al. described a case of successful omalizumab treatment in a girl with atopic eczema [80]. Park et al. published another more case with success [81]. In 2011, a case series reported three cases of severe AD patients who had elevated IgE levels and failed to response to several previous therapies. After being treated with omalizumab, the patients had marked alleviation of symptoms with improved Eczema Area and Severity Index (EASI) and pruritic score [82]. The same year, another case series with 11 patients with severe AD were treated with omalizumab, and all patients showed gradual improvement in SCORing Atopic Dermatitis (SCORAD) scores, decrease in symptoms, and an improvement in quality of life [83]. In 2012, Fernandez-Anton et al. treated with omalizumab nine patients with severe atopic dermatitis refractory to at least two systemic drugs. All patients reported a decrease in pruritus and an improvement in quality of life [84].

In 2013, Sanchez-Ramon et al. proposed a sequential therapeutic strategy with two monoclonal antibodies, omalizumab, and rituximab (anti-CD20). Authors reported six cases of severe AD refractory to conventional therapy. Four out of six patients achieved a spectacular clinical improvement with this novel approach [85]. In another study of ten patients with AD who received omalizumab for persistent asthma, there was an important improvement in the SCORAD [86]. No placebo group was included. In a randomized, double-blind, placebo-controlled study of eight patients with severe refractory AD, the patients of the omalizumab-treated group had an improvement in clinical outcomes as measured by the SCORAD system but comparable to improvements in the control group [87].

A case series has reported benefits with omalizumab plus intravenous immunoglobulin for severe AD [88]. In 2014, Hotze et al. conducted a prospective 28-week open-label trial on 20 adults with moderate-to-severe AD to evaluate the

efficacy of omalizumab in AD and to identify markers associated with treatment response. None of the seven patients carrying a filaggrin (FLG) mutation responded to therapy, while all eight responders were non-FLG-mutation carriers, indicating that patients with a primary skin barrier deficiency are less likely to benefit from an immunomodulatory treatment with anti-IgE. Responders are characterized also by the presence of high levels of various glycerophospholipids [89]. Heil et al. studied 20 AD individuals and concluded that the therapeutic benefit of omalizumab treatment, if present at all, would be seen more in acute AD patients rather than chronic forms of the disease. More randomized controlled trials should be performed to clarify the potential benefit of omalizumab for patients with atopic eczema. Only in case series without placebo control group, there is an evidence of effectiveness of omalizumab for AD.

Bullous pemphigoid (BP) is an acquired, autoimmune, bullous disease presenting with subepidermal blistering, eosinophilia, and severe itch that is characterized by autoantibodies against the 230-kDa bullous pemphigoid antigen within basal keratinocytes and the 180-kDa type XVII collagen within the basement membrane zone lying between the epidermis and dermis [90]. IgE antibodies specific for the BP180 autoantigen are detected in sera and biopsy samples from the majority of BP patients. A study in 2014 of BP biopsies, both IgE and BP180 antigen, localized on the surface of mast cells, and incubation of circulating basophils from these patients with BP180 protein triggered degranulation [91]. These findings have led to therapeutic trials of omalizumab in BP, resulting in substantial improvement in the patients' disease. But the first case reported with successful treatment of bullous pemphigoid with omalizumab was in 2009 [92]. Another case report in 2012 was published. A woman with pruritic BP and very high levels of IgE and eosinophils who was refractory to standard aggressive immunosuppressive regimens for BP but responded rapidly to systemic omalizumab [93]. Omalizumab has also showed effectiveness in infant BP [94]. Six patients treated with bullous pemphigoid using omalizumab and followed up their disease for up to 42 months showed variable therapeutic benefit with less use of other immunosuppressants, inhibition of new bullae, less pruritus, and dramatic decreases in eosinophilia [95]. This year too, Yalcin et al. published another case of a man with BP and very high levels of total IgE (5000 kU/L) who was refractory to standard aggressive immunosuppressive regimens (systemic steroids, daily cyclophosphamide) but responded rapidly to omalizumab [96].

Kimura's disease is a chronic disease that is characterized by subcutaneous granuloma of soft tissues in the head and neck region, increased eosinophil counts, and high serum IgE levels. Three patients with Kimura's disease received eight cycles of omalizumab 300 mg, administered subcutaneously at intervals of 2 weeks. In all

of the patients, the size of granulomas and the peripheral blood eosinophil counts were all decreased after the treatment [97].

Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency, usually characterized by a triad of increased serum IgE levels, recurrent skin abscesses and recurrent pneumonia, leading to pneumatocele formation. Patients are infected often with *Staphylococcus aureus*, *Candida albicans*, and certain viruses [98]. Omalizumab has exhibited benefit for skin lesions in a patient with HIES [99].

There are anecdotal and case reports of the use, with success or not, of omalizumab for diverse skin conditions such as severe delayed pressure angioedema [100] and urticaria [101], bullous urticaria [102], vibratory angioedema [103], occupational wheat contact dermatitis and baker's asthma [104], refractory heat urticaria [105, 106], solar urticaria [107, 108], and recurrent idiopathic angioedema [109].

Add-on Specific Immunotherapy

Several cases have been published about the use of omalizumab before specific immunotherapy since 2002. Omalizumab has been shown to enhance the safety and tolerability of immunotherapy, especially specific cutaneous immunotherapy (SCIT) and venom immunotherapy (VIT) but also sublingual immunotherapy (SLIT) [110]. This off-label use significantly reduced the risk of adverse events [111, 112]. In 2010, Massanari et al. carried out a multicenter, double-blind, parallel-group study with randomized patients treated with omalizumab or placebo, after which they received specific immunotherapy to at least one of three perennial aeroallergens (cat, dog, and house dust mite) [113]. The use of omalizumab in patients was associated with fewer systemic allergic reactions to specific immunotherapy and enabled more patients to achieve the immunotherapy maintenance dose. The same year, Tartibi et al. published the case of a patient being on immunotherapy for fire ant allergy. She had anaphylaxis after a fire ant sting as well as an injection of fire ant-specific immunotherapy. The patient underwent unsuccessful treatment with fire ant immunotherapy from both a safety and efficacy perspective but responded well to omalizumab [114]. In another case of fire ant sting allergy, the authors reported successful rapid fire ant desensitization using omalizumab in conjunction with an antihistamine and corticosteroid premedication regimen [115]. A group of investigators have been using omalizumab since 2005 in the rare cases of severe anaphylactic reactions during the initiation of the venom immunotherapy. While in the past this supposed stopping the specific immunotherapy, the current situation

has remarkably changed. A new therapeutic option for omalizumab is presented [116].

Food Allergy

From 2003, the efficacy of anti-IgE treatment in food allergy has been established increasing the tolerance to peanut in some individuals with peanut-induced anaphylaxis. Several studies have been conducted in peanut-allergic patients [117–119] and larger randomized placebo-controlled studies are at present being conducted to verify the usefulness of omalizumab in facilitating oral peanut desensitization. Savage et al. studying peanut-allergic patients discovered that the clinical response to omalizumab occurs early in treatment when the basophil, but not the mast cell, is suppressed, supporting a role for the basophil in acute food reactions [120]. In this study, authors concluded that basophil hyporesponsiveness to allergen assessed either as total inhibition of reactivity or as a shift in allergen sensitivity might be a biomarker of the changing threshold in the open-food challenges.

Omalizumab has been useful introducing oral immunotherapy in food-allergic patients. A pilot study in 11 children with cow's milk allergy showed the benefit of pretreatment with omalizumab from 9 weeks before and during a combined two phases: one ultrarush 1-day partial up dosing followed by a second phase further 16-week more slow up dosing phase. Omalizumab treatment was then discontinued at week 16, whereas daily oral milk was continued at home. Nine of 11 children were able to tolerate a DBPC food challenge 8 weeks after stopping omalizumab and to continue a daily intake of 8000 mg of dairy products. One patient was able to take 4000 mg, and there was only 1 treatment failure [121]. Begin et al. evaluated the safety and dose tolerability of a phase 1 single-site oral immunotherapy (OIT) protocol using omalizumab to allow for a faster and safe desensitization to multiple foods simultaneously in 25 patients [122]. Participants with various food allergies received OIT for up to five allergens concurrently with omalizumab. Omalizumab was administered for 8 weeks prior to and 8 weeks following the initiation of a rush OIT protocol. Nineteen participants tolerated up to 1250 mg of combined food proteins. There is a case report of a patient who, after a successful desensitization with egg using omalizumab as pretreatment, showed recurrence of symptoms after discontinuation of anti-IgE therapy [123]. Two multicenter, double-blind, placebo-controlled, phase II and III trials are in progress at two hospitals in the USA (Mount Sinai School of Medicine in New York and Duke University in North Carolina) with peanut- and milk-allergic patients, respectively [124].

Rocha et al. reported two patients with multiple food allergies and eosinophilic esophagitis on a very restrictive diet, who have been treated with omalizumab

[125]. The patients significantly improved in the allergic symptoms and quality of life, but the endoscopic and histological features of eosinophilic esophagitis did not change.

Anaphylaxis

Systemic mastocytosis is a disease characterized by a pathologic dysregulated accumulation of mast cells in tissues such as skin, gastrointestinal tract, bone marrow, liver, and spleen. A greater part of these adult patients have a point mutation in the c-kit gene at the 816 position (D816V) that is thought to contribute to the abnormal proliferation of mast cells and enhanced mast cell survival [126]. Mastocytosis patients who require VIT have an increased incidence of allergic reactions to VIT injections when baseline tryptase is elevated. Several case reports combining omalizumab with venom-specific immunotherapy to improve the safety of the latter in mastocytosis patients have been published [127–129]. Omalizumab has been reported to be safe and effective in preventing recurrent anaphylaxis in several small case series [130–135]. The patients showed rapid and long-term efficiency of this treatment to control life-threatening mastocytosis-related symptoms. It has been reported a successful treatment using omalizumab in a patient with both cutaneous mastocytosis and Meniere disease [136]. Curiously, the ability of omalizumab to decrease the frequency of episodes of anaphylaxis in systemic mastocytosis patients within a short time did not appear to rely on the ability of omalizumab to decrease mast cell numbers because the serum tryptase levels in these patients did not vary during the period of response [137]. The mechanisms underlying the symptomatic improvement of systemic mastocytosis patients treated with omalizumab are not fully understood.

A case report of the successful use of omalizumab in the treatment of exercise-induced-anaphylaxis (EIA) has been published, although the pathophysiology of EIA remains unknown [138]. But omalizumab might be considered as an alternative treatment to prevent anaphylactic events in patients for whom the causative agent(s) cannot be recognized or avoided [139–141].

Drug allergy

Patients with aspirin-exacerbated respiratory disease (AERD) have persistent asthma, chronic rhinosinusitis, and recurrent nasal polyposis. Aspirin desensitization is currently the only method that has demonstrated success

Table 1 Summary of the uses off-label of omalizumab

Respiratory disorders	Pregnancy women, total IgE <30 or >700 UI/ml, intrinsic asthma, allergic bronchopulmonary aspergillosis, allergic rhinitis, chronic rhinosinusitis, nasal polyps Churg-Strauss Syndrome, eosinophilic pneumonia, occupational asthma, angioedema of the larynx
Skin diseases	Atopic dermatitis, bullous pemphigoid, Kimura's disease, Hyper-IgE syndrome, delayed pressure angioedema and urticaria, bullous urticaria, vibratory angioedema, occupational wheat contact dermatitis and baker's asthma, refractory heat urticaria, solar urticaria and recurrent idiopathic angioedema
Add-on specific immunotherapy	
Food allergy	Allergy to peanut, milk and egg, eosinophilic esophagitis
Anaphylaxis	Mastocytosis, exercise-induced anaphylaxis
Drug allergy	Aspirin, latex, insulin, carboplatin
Ocular diseases	Vernal conjunctivitis
Ear disorders	Eosinophilic otitis media

in modifying the natural course of this disease; it prevents regrowth of nasal polypoid tissue, achieves better asthma control, and allows the patient to take any cyclooxygenase-1 (COX-1) inhibitor [142]. Omalizumab could be effective in the treatment of AERD, as published Bobolea [143] and Aksu [144], who not only succeeded in controlling the disease and significantly improving the quality of life of a patient with AERD who was also capable of tolerating aspirin and other COX-1 inhibitors.

Omalizumab has limited evidence for efficacy in healthcare workers with occupational latex allergy [145]. Omalizumab has been used successfully in cases of insulin allergy [146–148] in which, although patients initially gained tolerance through a desensitization procedure, finally insulin allergy reappeared. Omalizumab allowed the administration of carboplatin, a chemotherapeutic agent that is frequently used in the management of ovarian cancer, in a carboplatin-allergic patient with a serous adenocarcinoma of ovarian, who responded appropriately [149].

Ocular Diseases

Vernal keratoconjunctivitis (VKC) is a severe ocular disease with immediate and delayed hypersensitivity reactions which can produce loss of visual acuity and blindness. VKC belongs to the group of allergic eye diseases [150] but conventional therapy for allergic

conjunctivitis is generally not adequate for VKC [151]. However, Sanchez and Cardona published a case report of a 16-year-old male patient with VKC with no response to conventional therapy but with important improvement in clinical symptoms after beginning omalizumab [152]. In 2013, another case, a 12-year-old boy with severe mixed limbal and palpebral vernal keratoconjunctivitis improved with omalizumab treatment, was published [153].

Ear Disorders

EOM, first described by Matsutani et al. in 1995, is an intractable otitis media characterized by heavy eosinophilic infiltration and high viscous mucoid effusion [154], and it is found in 90 % of patients with adult-onset asthma [155]. A case report of a patient with severe asthma and concomitant intractable EOM, in which omalizumab therapy improved the symptoms of both asthma and EOM, was published in 2012 [156]. Authors indicated that “early initiation of omalizumab therapy may inhibit the progression of complicated EOM.” A study of eight patients with EOM who received omalizumab for at least 3 months showed improvement of their clinical scores with disappearance of the middle ear effusion (MEE) [157]. The same authors observed that eosinophil cationic protein (ECP) concentrations in MEE in patients with EOM were significantly decreased at 3 months after the administration of omalizumab from the baseline level ($p < 0.05$) [158].

In the Table 1, the off-label uses of omalizumab are summarized.

Conclusions

This article has tried to review as widely as possible the up-to-date off-label use of omalizumab but some publications could have been overlooked. We need to know more about the factors that produce off-label medication use. Of course, a therapeutic need is the first factor to consider. Off-label uses could become licensed indications in the future. The success in exploring the effect of omalizumab as alternative therapy in other diseases different to asthma, such as occurred with chronic urticaria, will lead to new treatments for this and other diseases preventing complications, with a decrease in general healthcare cost in the long term. It is difficult to connect off-label medication use to promotional activities for specific off-label indications. We need to understand the promoters of off-label medication use, including the influence of pharmaceutical industry.

While at present, only one biological (omalizumab) is licensed in chronic urticaria, there is expectation that more anti-IgE molecules will arrive. We hope that the knowledge of the mechanism of action of these drugs will also arrive soon.

Conflict of Interest The author declares that there is no conflict of interest.

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