CLINICAL INVESTIGATION

Omalizumab for the treatment of atopic dermatitis

Atopic dermatitis (AD) is a common inflammatory skin disease with hyper-reactivity to environmental triggers in predisposed individuals. Type 2 helper T cells driven inflammation is prevalent in early phases while Th1/Th17 mechanisms lead the chronic forms. Omalizumab is a monoclonal anti-IgE antibody that is approved in many countries for the treatment of some asthma and urticaria patients. Several reports have highlighted the efficacy of omalizumab in AD patients. We describe herein a series of 12 AD patients treated with omalizumab, six of which obtained significant clinical benefit. Controlled trials include only small number of AD patients and have not found differences with placebo, although an effect of omalizumab over the immunological responses to allergens might exist. More studies are warranted to elucidate whether specific subgroups of AD patients could obtain benefit from omalizumab.

Keywords: atopic dermatitis • IgE • omalizumab

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Atopic dermatitis (AD) is a recurrent inflammatory skin disorder that affects up to 3% of adults and 15–20% of children in the Western World [1]. Diagnosis consists on clinical evaluation of signs and symptoms [2]. Eczematous lesions together with pestering itch are considered hallmarks of the disease [2] and lead AD patients to suffer from a chronic loss of sleep and concentration with significant impairment of their quality of life [3]. Acute AD is characterized by erythematous and exudative lesions, whereas the chronic form is characterized by lichenification and crusting [2]. This clinical dualism has been correlated with a parallel dual immunopathological pattern, with Type 2 helper T cells (Th2)-driven eosinophilic inflammation prevailing in the acute phase and Th1/Th17 mechanisms leading the chronic forms of the disorder [4].

Pathogenesis of atopic dermatitis

Intrinsic factors

Clinical heterogeneity in AD is not just restricted to the different time points of the ongoing inflammation. Nowadays AD is considered a heterogeneous clinical phenotype rather than a uniform disease [4], in which different isolated or coexisting factors can induce resembling clinical outcomes. Several genetic modifications have been described to date in AD patients. They include not only the better-studied mutations in the filaggrin gene, but also alterations in other genes like the ones encoding S100 proteins, small proline-rich proteases or tight junction proteins. [5,6]. All these changes affect the differentiation and function of keratinocytes and promote a skin barrier dysfunction with an increased epidermal water loss among other abnormalities [7]. The role of genetics in AD pathogenesis goes beyond effects on epidermal proteins. Several polymorphisms in genes encoding proteins with important immune functions such as IL-4, IL4R or IL-13 have been reported to promote AD by favoring a Th2-polarization [8]. Interestingly, IL-4, IL-13, the Th2 polarizing factor thymic stromal lymphopoietin (TSLP) and histamine have been shown to regulate kera-

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tinocyte function [9,10], rising up the possibility of an immune-driven impairment of skin barrier function. Other intrinsic abnormalities might also play a role in the disorder. Higher numbers of both Langerhans cells and inflammatory dendritic epidermal cells expressing the high-affinity receptor for IgE (FcεRI) have been reported in AD, even in the apparently noninflamed areas of the skin [11].

Extrinsic factors

Nevertheless, cutaneous hyper-reactivity to environmental triggers is also involved in AD pathogenesis. The role of food and aeroallergens has been pointed out in recent years in a subset of AD patients [12]. The effects of these triggers could be partially explained by the intrinsic immune dysregulation of AD patients as illustrated by the reported defect in the suppressive activity of naturally occurring CD4+CD25+FoxP3 regulatory T cells [13]. However, some nonallergenic pollen-derived substances have been shown to promote mast cell activation by both IgE-dependent and -independent mechanisms [14]. Furthermore, some house dust mite allergens display protease activity and are able to disrupt intercellular junctions [15] and activate several innate immunity receptors [16]. Food allergens, such as milk and egg have been related to AD exacerbations especially during early childhood [17]. In any case, the most prominent extrinsic factors influencing AD seem to be microbial molecules. IgE against *Malassezia furfur* is regularly found in patients with a history of long-lasting eczema [18] and has been related to a specific pattern of lesion distribution [19]. *Staphylococcus aureus* colonizes frequently AD skin [18] and the ability of its enterotoxins to polyclonally activate T cells with subsequent release of huge amounts of IgE and other immunoglobulin isotypes is well established [20]. Of note, IgE directed against enterotoxins is a common finding in AD [18]. *Staphylococcus aureus* might also influence the natural course of the disease. Some of its products down-regulate FcεRI expression on dendritic cells [21] and the staphylococcal enterotoxin B strongly promotes the secretion of Th17/Th22 cytokines [22,23]. These factors could explain partially the switch seen in chronic AD lesions toward a Th1/Th17 profile.

Autoimmune phenomena

Regardless of the relative contribution of the previous aspects, chronic AD lesions display a complex inflammatory infiltrate with Th17 and Th1 cytokines (IL-17 and IFN-γ, respectively) and tissue remodeling factors (TGF-β and thymus and activation-regulated chemokine, TARC) coexisting with eosinophil mediators and FcεRI positive cells [24,25]. In this inflammatory setting, sensitization to self-proteins is not uncommon and some of the IgE produced by these patients is actually directed against skin autoantigens [26]. Although these IgE autoantibodies are not always associated with clinical manifestations [27], some authors consider them as indicative of other immune mechanisms of self-sensitization, such as self-reactive IgG-producing B cells or autoreactive CD8+ T-cells [26]. Molecular mimicry of various microbial agents could also contribute to these autoimmune phenomena [28].

In summary, in AD many potential intrinsic and extrinsic factors differently combined lead to a Th2-driven skin inflammation characterized by a dense infiltrate with spongiosis. These initial changes under the influence of some extrinsic triggers can evolve to a chronic fibrotic lesion with less but more complex cellularity [4].

Current strategies for the treatment of atopic dermatitis

Standard therapy

AD is also a heterogeneous disorder in terms of prognosis and severity [29]. In some cases, disease simply resolves with time, whereas other patients can achieve control with exclusive use of topical treatment (corticosteroids and/or calcineurin inhibitors) and/or hygienic measures [30]. The later includes adequate skin hydration and the identification and elimination of flare factors such as irritants, allergens, infectious agents or emotional stressors, addressing thus the itch–scratch circle and protecting and reinforcing the skin barrier [31]. Nevertheless, an appreciable number of patients will require systemic therapy at some time point of their disease course [32]. Taking into account the complex pathophysiology and interfering factors in AD, it is not surprising that drugs with broad immune inhibitory actions are first line therapy in severe cases [32]. Systemic corticosteroids are frequently used for eczema exacerbations and sometimes also for maintenance therapy [32]. The consequences of long-lasting regimens with high-dose corticosteroids are well studied in the medical literature [33] and, of note, many patients in published studies of severe AD report some extent of adverse side effects due to corticosteroids. When a corticosteroid sparing therapy is necessary, oral cyclosporine is usually prescribed [34]. Cyclosporine is a calcineurin inhibitor able to decrease T-cell growth and activation and interfere consequently with B-cell activation, disabling both humoral and cellular arms of the immune response [35] and to date is the only approved drug for systemic use in AD beyond corticosteroids. However, AD patients are not always responsive to cyclosporine [36] and severe side effects including life-threatening infections, hypertension and nephrotoxicity may force the discontinuation of the drug [37]. The

conjunction of these facts, make the search for alternative medications to treat AD an interesting field of investigation.

Other therapeutic strategies

Virtually all classic broad-spectrum immunosuppressors have been tried in severe AD including azathioprine, tacrolimus, mycophenolate mofetil, methotrexate, intravenous immunoglobulins or plasmapheresis [38–42]. The rate of success with these therapies is in general unsatisfactory and although the quality of the published studies is not sufficient for definitive conclusions, safety issues with some of them are still a major concern [30]. PUVA therapy has been also suggested in AD [43], but the risk of skin cancer induction and the high work absenteeism related to its use limits the prescription of this therapeutic strategy. As our understanding of immune dysregulation of AD increases, new immunomodulatory drugs (especially biologicals) are emerging in an attempt to block specific mechanisms of disease development while preserving the global functionality of the immune system and decreasing thus the rate of side effects [32]. In this regard, studies using biologicals approved for other immune-mediated diseases have been performed including mepolizumab (anti-IL-5), rituximab (anti-CD20), etanercept or infliximab or adalimumab (anti-TNF-α), ustekinumab (blocks IL-12 and IL-23 necessary for Th1 and Th17 differentiation, respectively), tocilizumab (anti-IL-6R) or efalizumab (anti-CD11a), among others [44–52]. In general, these studies lack a proper design and even though there might be a role for some of these drugs in AD therapy (six of six patients improved in a pilot study with rituximab) [45], the above described multifactorial etiology makes unlikely the possibility of disease full resolution in a majority of patients by interfering exclusively one of the multiple arms of the immune system. Indeed, some of these immunomodulators are not exempt of severe adverse side effects [51], as illustrated by the risk of progressive multifocal leukoencephalopathy associated to efalizumab [53], which finally led to the withdrawal of the drug in 2009.

Omalizumab, anti-IgE therapy

Drug features

Among all the currently available biological therapies, probably the one that has gained most attention from researchers and clinicians is omalizumab (Xolair®, Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, CA, USA) [54]. Omalizumab is a humanized monoclonal antibody with CDR (complementarity determining regions) from mouse origin (<5% of all residues) linked to the structure of human IgG1 (>95% of residues) [55]. The molecule binds specifically to the third constant domain of the heavy chain of the human IgE in the Fc region [56], thus competing with IgE specific receptors (FcεRI and low-affinity IgE receptor, CD23) that also bind to IgE by Fc region [57,58]. This specificity of omalizumab is of great importance, since although the possibility of treating allergic diseases with anti-IgE antibodies was theorized back in the 70s [59], the cell activation ability of antibodies directed against the variable regions of IgE prevented this approach to reach clinical practice. Omalizumab does not affect the IgE that is already attached to its specific receptors on cell surface but when administrated in molar excess (15–20:1) forms relatively small immune complexes with free IgE (trimers of 500 kDa) that are eliminated by Fcγ receptors of the hepatic sinusoidal endothelial cells without sedimentation or activation of complement system [60]. Since IgE terminal half-life (1–2 days) [61] is considerably shorter than the one displayed by omalizumab (19–22 days) [60], upon initiation of therapy there is a quick increase of total IgE together with a decrease of free IgE that returns to baseline levels several months after discontinuation of the therapy [62]. This long terminal average half-life allows in turn lengthening the interval between doses [62].

Current uses of omalizumab

Omalizumab was first approved by the US FDA in 2003 and by European Medicines Agency (EMEA) in 2005 for the treatment of patients over 12-years old with noncontrolled severe persistent allergic asthma with proven sensitization to at least one perennial aeroallergen and reduced pulmonary function (FEV_1 <80%) despite treatment with high dose inhaled corticosteroids plus one inhaled long-lasting β_2 agonist. The drug was also included in the Global Initiative for Asthma guidelines from 2003 [63]. In 2009, omalizumab use was approved also for children between 6 and 12 years of age with similar indications. The drug is administered subcutaneously every 2–4 weeks in doses according to the weight of the patient and the serum baseline level of IgE [64]. The administration of omalizumab is not recommended for patients with baseline IgE levels exceeding 1,500 UI/ml irrespective of weight [64]. Given the central role of IgE in Th2-driven inflammation, clinicians and researchers started to use omalizumab for the treatment of allergic disorders and other diseases with resembling inflammatory pattern, shortly after the commercialization of the drug [54]. In this regard, articles reporting omalizumab use for allergic bronchopulmonary aspergillosis, IgE-mediated anaphylaxis and other forms of drug and food allergies, eosinophilic esophagitis, nasosinusal

polyposis, Churg–Strauss syndrome, physical urticaria or mastocytosis were published [65–73]. Omalizumab ability to improve tolerance to allergen-specific immunotherapy has been also tested with some success [74,75]. Even though anti-IgE therapy seems promising for some of the previous conditions (importantly nasal polyposis), there is not enough evidence yet for a general recommendation and cost–effectiveness is still a major concern [54]. Importantly and despite not being considered an IgE-mediated disease [76], chronic spontaneous urticaria (CSU) is an exception to the previous statement. Sufficient body of evidence supported omalizumab cost–effectiveness [77] and the drug was finally approved for CSU in 2014 and included in the guidelines [78] for the treatment of patients who do not respond to H1-antihistamines.

Rationale for omalizumab use in atopic dermatitis

Given the preponderance of eosinophilic infiltrate at least during the early stages of AD, it is not strange that this condition was among the first off-label uses of omalizumab [79]. The rationale for its use comes directly from the central role of IgE in Th2-driven inflammation [61]. Functional IgE is released by mature B cells after isotype class switching (either from mu or from gamma to epsilon) and somatic hypermutation processes [80]. Several transcription factors (STAT6) and cytokines (IL-4, IL-13, IL-25, IL-33, TSLP etc.) favor IgE synthesis [80]. Biological functions of IgE are exerted through the two surface receptors that have been described to date, FcεRI and CD23 [81].

FcεRI-mediated cell activation

FcεRI belongs to the Fc family of immunoglobulin receptors and displays the highest affinity (K_d: 1×10^{-10}) among all Fc receptors for its cognate ligand [57]. This means that in homeostasis, all FcεRI receptors are occupied by IgE [57]. The receptor is expressed as a tetramer (α chain with the single binding site for IgE, β chain and two γ chains with intracellular immunoreceptor tyrosine-based activation motifs, ITAMs) on the surface of basophils and mast cells [57]. When two or more FcεRI-IgE complexes are cross-linked by a single polyvalent antigen molecule, these cells become activated and start to release both preformed mediators (such as histamine and tryptase) and newly synthesized pro-inflammatory substances (leukotrienes and cytokines) [82]. A trimeric form of the receptor (lacking β chain) is also expressed by some antigen-presenting cells (APC) such as dendritic cells (DCs) and monocytes, and upon cross-linking is able to internalize and process the antigen with subsequent presentation of new epitopes to T cells [83]. This IgE-facilitated antigen presentation has been shown to be 100- to 1000-times more efficient than common antigen presentation by APC [83]. Anti-FcεRI IgG antibodies (seen for instance in autoimmune urticaria) and some molecules like galectin-3 that are overexpressed in inflammatory milieu can also activate mast cells and basophils via FcεRI in an IgE-independent manner [84,85]. Although this finding could lead to consider FcεRI as the key player of Th2 inflammation, the fact is that the most potent inducer of FcεRI expression is actually IgE, that stabilizes the receptor on cell surface [57] and is thus crucial for both IgE-dependent and independent mechanisms of FcεRI activation.

CD23-mediated cell activation

IgE also binds to the protein CD23, which belongs to the C-type lectin superfamily of adhesion molecules [81]. As a surface protein, the extracellular part of CD23 is basically comprised by three lectin 'head' domains attached to the membrane by an α-helical stalk region that has a MHC-II binding site [81]. Each lectin domain possess a binding site for IgE and even though the affinity of a single head is low, after correcting for the avidity factor the overall affinity approaches the one of FcεRI (K_d:$1 \times 10^{-8/-9}$) [86]. Calcium-independent IgE binding to membrane CD23 in mature B cells provides inhibitory signals for further IgE synthesis [86]. However, some allergens or pro-inflammatory molecules (such as ADAM10) can cleave the stalk region, releasing thus the soluble form of CD23 [86,87]. This soluble receptor is able to upregulate IgE synthesis by colligation of CD21 (its other cognate ligand) with membrane IgE on B-cells in a calcium-dependent manner [86]. Of note, this second scenario resembles more the tissue environment in AD and other allergic diseases. The interaction between CD23 and HLA-DR in the membrane of B cells also promotes the internalization of antigen-IgE complexes, favoring thus antigen presentation to T cells [88]. The receptor is also constitutively expressed in the luminal membrane of mucosal epithelial cells [89]. The binding of soluble IgE-antigen complexes to membrane CD23 in the respiratory or digestive mucosa produces the transcytosis of the antigen, preventing thus its intracellular processing and allowing allergens to gain access to IgE-bearing subepithelial mast cells in an intact manner [89,90].

Theoretically, by interfering IgE binding to its cognate receptors (for instance using omalizumab that binds to IgE Fc region), mast cell and basophil activation, IgE-facilitated antigen presentation by APC and B cells and allergen transcytosis through epithelia are being directly antagonized. IgE blockade by omalizumab has been shown to downregulate FcεRI expression on cell surface and indirectly would inhibit

also IgE-independent FcεRI-dependent mast cell and basophil activation. All these omalizumab anti-inflammatory effects would diminish further isotype class switching to IgE and subsequently soluble CD23-dependent IgE synthesis by B cells would also decrease. A summary of all these effects can be seen in Figure 1.

Evidence for inhibitory effect of omalizumab over inflammation

Most of the above mentioned biological functions of IgE are believed to play a role in the pathogenesis of AD and other allergic diseases [4]. However, direct evidence supporting the inhibitory effect of omalizumab over the described mechanisms is sparse and mainly focused on bronchial asthma. In a controlled study of eosinophilic persistent asthma, omalizumab treated group showed a significant decrease in the number of IgE, FcεRI, CD3, CD4, CD8, IL-4-positive cells and B cells in the airway mucosa, together with a reduction of eosinophils in both sputum and tissue [91]. Another controlled study of patients with nonatopic asthma showed a decreased FcεRI expression on blood basophils and APC in omalizumab-treated individuals [92]. As in AD, polyclonal T-cell activation by *S. aureus* has been related to the pathogenesis of nasal polyps and intrinsic asthma. A study in 2007 suggested a lower recurrence rate after polypectomy in some patients treated with omalizumab [93]. On the other hand, anti-IgE therapy did not seem to affect antigen presentation since the administration of omalizumab did not modify allergen-specific T-cell responses in eosinophilic esophagitis patients [94]. A controlled pilot study for assessing omalizumab performance in AD reported a decrease in the expression of surface IgE and FcεRI in peripheral blood mononuclear cells, a reduction in the saturation of FcεRI with IgE and a decrease in the number of IgE positive, but not FcεRI positive cells in skin [95]. In another controlled study of children with severe AD, TSLP and TARC levels were significantly reduced in the omalizumab-treated group [96].

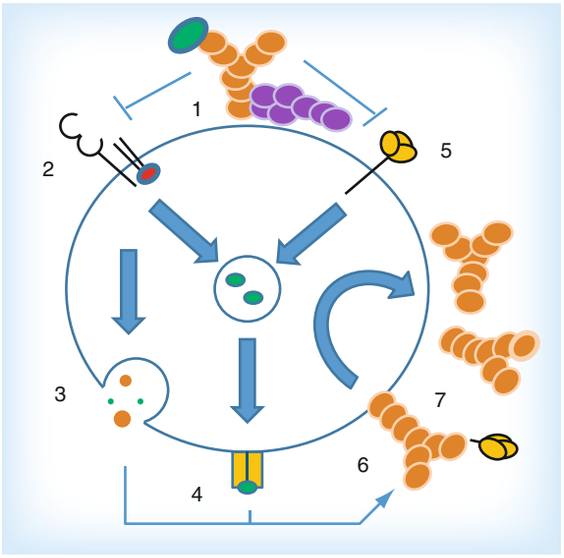

Figure 1. Omalizumab effects on IgE-mediated Inflammation. The binding of omalizumab (in purple) to the Fc region of IgE (in orange) (1) inhibits IgE binding to FcεRI and also FcεRI expression on cell surface (2). This inhibition blocks FcεRI-dependent release of pro-inflammatory mediators by basophils and mast cells (3) and IgE-facilitated antigen presentation by antigen-presenting cells (4). Omalizumab also inhibits the binding of IgE to CD23 in the membrane of B cells (5). This inhibition also decreases IgE-facilitated antigen presentation by B cells (4). The blockade of all these inflammatory processes (3 & 4) will decrease in turn further isotype class switching towards IgE (6). The reduction in IgE-expressing B cells will also diminish soluble CD23-dependent IgE synthesis by B cells in inflammatory milieus (CD21 also required but not shown) (7).

Clinical evidence regarding omalizumab use for atopic dermatitis

Early noncontrolled studies

The first article reporting omalizumab use for AD was published in 2005 and described the failure of the drug for treating three adult patients [79]. This study was preceded by several reviews theorizing the ability of omalizumab to improve atopic conditions such as AD [97]. However, many case reports and small case series since 2005 have reported beneficial clinical outcomes in adult AD patients treated with omalizumab in monotherapy [98–101]. Additionally, some studies in asthmatic adult patients have reported concomitant eczema improvement by omalizumab. A deeper analysis of the literature reveals high variability in terms of therapy response, with only some patients showing highly significant changes [100]. The interpretation of these articles is complicated, since most of the published studies focused exclusively on long-lasting severe to recalcitrant eczema patients [98], with almost no study investigating the effect of omalizumab in earlier or milder stages. Indeed, most of the patients included had taken strong immunosuppressors shortly before inclusion [99], or took rescue medication during the course of the study [100]. Furthermore, the different doses and protocols used by the different authors make articles even more difficult to compare. Most AD patients have high levels of serum IgE [4], and it is not uncommon that these levels exceed the recommended limit for prescription of omalizumab [64]. Authors tend to choose regimens with the doses and intervals recommended by the manufacturer for bronchial asthma [98–101], referred from now as high doses. Even though one study reported clinical improvement in six of 11 AD patients treated with

Table 1. Medication score.

Punctuation	Medicines
1	Oral antihistamines or antileukotrienes
2	Topical tacrolimus or pimecrolimus
3	Topical corticosteroids
4	Oral corticosteroids, cyclosporine, methotrexate, azathioprine, diazepam or antibiotics. Phototherapy
+0	Intermitent/low dose
+1	Continuous/high dose

A different punctuation according to safety profile and impact on patient's quality of life was assigned to every drug that had been used by the patients before the initiation of omalizumab. Additionally, one extra point was added to every medication that was being administered at high doses or on a regular basis (in comparison to intermittent use or low doses).

lower doses of the drug [102], the first negative report from 2005 [79] was actually criticized for using low doses [103]. In a more recent pilot study, 21 adult patients with AD were stratified according to their baseline level of IgE and received different doses of omalizumab. Interestingly, all of them showed significant improvement of their clinical AD scores [104].

Authors' experience on omalizumab for atopic dermatitis

The protocol used in our centre for treating AD patients with omalizumab is described herein.

Selection of AD patients for anti-IgE therapy

Anti-IgE therapy is considered in AD patients over 12 years of age that need systemic broad-spectrum immunosuppressors for disease control or in subjects that have been on topical therapy for more than one year and present other atopic comorbidities. Disease control is defined as the absence of visible skin lesions. No patients with autoimmune diseases, immune deficiencies or malignancies are included. Before beginning treatment, all patients are informed about off-label use of the drug and sign informed consent. Additionally, a Hospital Committee in charge of examining off-label prescriptions must approve the use for every single patient. When IgE baseline level is <1500 UI/ml the dose indicated by the manufacturer is administered and in the rest of the cases a medium-to-high dose according to the weight is prescribed.

Follow-up of AD patients on anti-IgE therapy

The clinical response to omalizumab is determined as the decrease in the requirements for other medications to maintain disease control upon initiation of the therapy. In an attempt to objectively evaluate this variable we have designed a medication score (MS) (Table 1). MS and treatment step of 2006 PRACTALL Consensus Report for diagnosing AD [105] are calculated for every patient before initiation of the therapy. The discontinuation of every medication taken by the patients before the initiation is tried during the course of the therapy and MS and PRACTALL score are measured again 3 months after the first dose of omalizumab. Omalizumab is maintained if a clinical response is found, otherwise the therapy is discontinued.

Response to anti-IgE therapy in our series of AD patients

Twelve subjects (eight men/four women) have been enrolled to date with ages ranging from 12 to 44 years. Patient characteristics are described in Table 2. All the patients showed decreases in their MS during the first three months of therapy (Figure 2) and in half of them the reduction exceeded the 10 points (patients 1, 3, 9, 10, 11 and 12 of Table 2). The subjects with higher MS before treatment (and more severe baseline disease) obtained a more marked benefit, even though an individual with a low pre-MS achieved control with no medication but omalizumab (patient 5 of Table 2). Anti-IgE therapy was maintained in all the patients beyond 3 months, although in three individuals (patients 1, 3 and 8 of Table 2) circumstances nonrelated with the drug forced to extend the interval between doses from 2–4 to 3–6 weeks. No worsening of the skin conditions was observed. One subject (patient 9 of Table 2) developed a flare-up 8 months after initiation of the therapy and omalizumab discontinuation was decided. The rest of the patients maintain long-term disease control (up to 3 years in one case, patient 1 of Table 2) with omalizumab therapy and no adverse side effect attributable to the drug has been reported to date.

Discussion on the response to omalizumab in our series of AD patients

In our series, individuals with higher pretreatment MS tended to have higher IgE levels, which is concordant with the more severe phenotype previously reported for these patients [8]. Of note, there was a good correlation between PRACTALL Consensus steps and MS in most of the patients, even though the later method better discriminated the patients within the higher scores. Importantly, clinical response was not associated with a decrease in the level of IgE in all the patients (data not shown), as had been reported previously in some other studies [106]. Despite some degree of improvement in all the patients of our series, only some of them achieved significant clinical benefit from omalizumab.

This finding is concordant with the highly variable clinical response observed in the noncontrolled studies and suggests that differences between AD patients may exist in terms of anti-IgE responsiveness.

Controlled study in monotherapy & prediction of omalizumab response

The above-mentioned literature likely suffers from several biases including the well-established placebo effect of systemic nonoral therapies for skin diseases and the trend to not report unsuccessful therapeutic approaches. Indeed, these studies do not take into account the recovery-relapse nature of AD [4]. Some of these biases are probably minimized in the only double-blind placebo-controlled study published to date assessing the performance of omalizumab in adult patients with AD [95]. Twenty patients with active disease were randomized to receive either drug or placebo. Omalizumab dose was calculated according to the weight and baseline IgE level that exceeded in some cases the limit recommended by the manufacturer. No differences were observed in the measured clinical outcomes, but significant decreases in the skin prick test and atopy patch test responses to relevant allergens were seen in some active-treated patients [95]. This observation might imply a role for omalizumab in some cases of AD with high allergen-dependency (and probably a Th2 predominant inflammation). This is also consistent with the data reported in the noncontrolled literature where some omalizumab-treated patients showed impressive improvements otherwise difficult to explain [100]. This hypothesis is also concordant with our own experience of one adult patient (patient 1, Table 2) with severe AD (SCORAD 47) and a phenotype highly dependent on house dust mites sensitization that achieved long-term full resolution of his eczema (SCORAD 0) with omalizumab therapy. In this regard, a recent open-label trial on 20 adult patients with moderate-to-severe AD tried to determine predictive factors for omalizumab responsiveness [107]. Even though the small number of subject included in the study limits the interpretation, the drug-responder subgroup was found to have an altered lipid metabolites profile and absence of filaggrin mutations. Imbalance in lipid signalling pathways are known to contribute to chronic inflammation like allergy [108]. Even though conclusive evidence regarding the effectiveness of omalizumab in AD is lacking, some subjects seem to obtain benefit from the drug. In this regard, responder subjects could display a disease phenotype highly dependent on extrinsic allergen sensitization and reactivity, whereas nonresponder individuals would have a more important contribution of other disease mechanisms (e.g., filaggrin mutations).

Uses in combination with other drugs

Given the heterogeneity of AD in terms of pathogenesis and clinical course [2], it is not surprising that not every patient respond equally to a given therapy, especially when using drugs with inhibitory effect restricted to specific arms of the immune system. Interestingly, omalizumab was proven very effective in the reduction of asthma exacerbations [91,92], while its effect over other clinical outcomes of the disease is less pronounced. A clinical trial using anti-IL-13 therapy for bronchial

Table 2. Clinical and analytical features of our series of 12 atopic dermatitis adult patients.

Patient	Sex	Age (years)	Comorbidities	Total IgE (UI/ml)†	Dose (mg)	Week between doses	Months on therapy	DR	TDR
1	Male	38	FA	25,000	450	4	36	Yes	Yes
2	Male	37	ARC, BA, FA	6214	450	2	16	No	
3	Male	34	None	3012	450	2	12	Yes	Yes
4	Female	40	FA	943	600	2	3	No	
5	Male	35	ARC, FA, ChU	4956	375	2	14	No	
6	Female	31	ARC, BA	8690	300	2	7	No	
7	Male	12	ARC, BA	196	300	2	4	No	
8	Male	39	ARC, BA	12,089	450	2	14	Yes	Yes
9	Female	44	ARC, FA, CSU, ACD	5444	450	2	8	No	
10	Male	30	BA	35,770	450	2	12	No	
11	Female	43	ARC, BA, FA	9440	450	2	14	No	
12	Male	23	ARC	2307	450	2	17	No	

†At baseline.

ACD: Allergic contact dermatitis; ARC: Allergic rhino-conjunctivitis; BA: Bronchial asthma; ChU: Cholinergic urticaria; CSU: Chronic spontaneous urticaria; DR: Dose reduction; FA: Food allergy; TDR: Tolerance to dose reduction.

asthma also suggested that the patient's phenotype is crucial for predicting responsiveness to immunomodulatory therapies when used for complex inflammatory diseases [109]. One solution for overriding this limitation would be the co-administration of various immunomodulators with inhibitory effects over different arms of the immune response [110]. This synergistic approach is commonly used by clinical immunologists to treat transplanted patients and other individuals with immune-mediated diseases and shows a reasonable safety profile [111]. One study reported improvement in three of four adult patients receiving low doses of omalizumab and intravenous immunoglobulin for AD [112]. One of the responder subjects was also on methotrexate therapy. In a single-centre observational study published by our group, four of six adult patients with severe AD refractory to conventional therapy were successfully treated using a sequential combined therapy with omalizumab and rituximab [113]. High doses of both drugs were administered. Of note, the three patients that received firstly rituximab took 3 to 4 weeks longer to achieve a significant benefit than those pretreated with omalizumab. This observation might indicate that the pre-inhibition of Th2-inflammation by anti-IgE therapy might facilitate the depletion of B cells by rituximab that would abolish in turn the synthesis of autoantibodies (of both IgE and IgG isotypes) and the B- and T-cell co-stimulation [113]. The capacity of rituximab to decrease also the level of neutralizing antibodies against biological drugs [114] could additionally enhance the efficacy of omalizumab in this setting. Overall, these findings suggest that some AD patients with absent or nonsustained response to omalizumab could have a more complex disease (with more interfering pathological mechanisms) than omalizumab responders. Some of them might be rescued from treatment failure by adding drugs with synergistic actions [113].

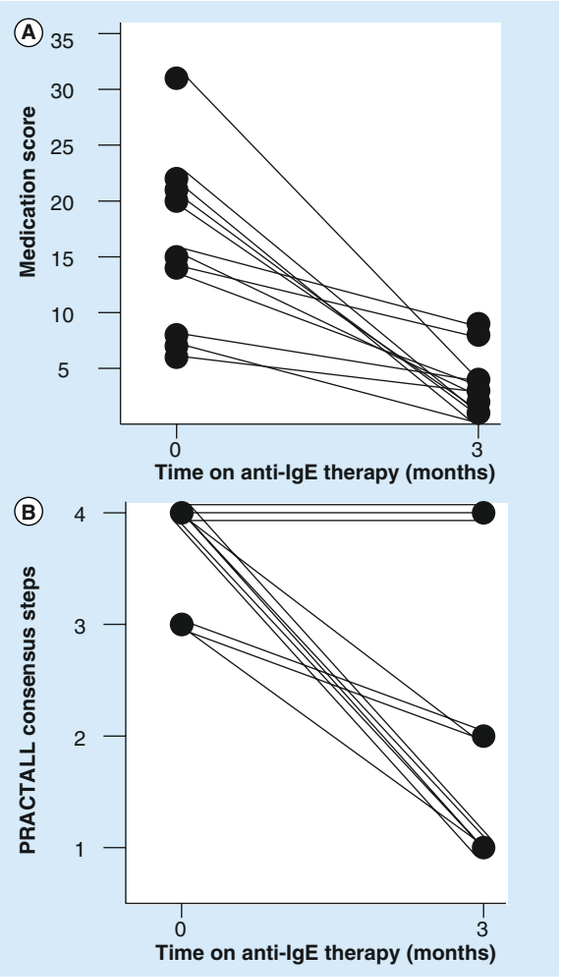

Figure 2. Changes in the requirements of medication for disease control in our series of 12 atopic dermatitis adult patients. (A) Medication score measured at baseline and 3 months after the first dose of omalizumab. **(B)** Steps of PRACTALL Consensus for Atopic Dermatitis at baseline and 3 months after the first dose of omalizumab [105].

Pediatric use

Many AD adult patients were diagnosed during childhood [4] and, beyond the greater relevance of food allergen sensitization in the first years of life [12], disease pathogenesis is quite similar at any age. However, the existing concerns for the use of classic immunosuppressors in children make the therapy of AD even more challenging during this age range [115]. Omalizumab was promptly postulated as a putative therapy for paediatric AD due to its presumably good safety profile. In a placebo-controlled clinical trial of eight AD patients with ages ranging from 4 to 22 years the active group received high doses of omalizumab. An improvement in SCORAD system that was comparable between the two randomized groups was found [96]. An article from 2013 reported five pediatric patients [6 to 11 years-old] with refractory AD to cyclosporine and azathioprine that were successfully treated with high doses of omalizumab [116]. In our experience the effect of omalizumab over AD during childhood (patients between 5 and 12 years old) shows the same interpatient variability than during adulthood. Good quality evidence supports the safety of omalizumab in children over 6 years old as can be deduced from large-scale clinical trials in pediatric asthma [117].

A summary of selected literature on omalizumab treatment for AD can be seen in Table 3.

Assesment of effectiveness & duration of omalizumab treatment for atopic dermatitis

Available evidence is not sufficient for a general recommendation regarding the duration of omalizumab

Table 3. Selected literature on omalizumab for atopic dermatitis.

Study	Year	Included subjects	Baseline disease	Dose†	Significant improvement‡	Notes	Ref.
Noncontrolled studies in monotherapy							
Krathen *et al.*	2005	Three adults	Severe	Low	No patient		[76]
Lane *et al.*	2006	Three patients (10–13 years)	Severe	High	Three of three patients		[95]
Belloni *et al.*	2007	11 adults	Severe	Low	Two of 11 patients		[99]
Fernández-Antón *et al.*	2012	Nine adults	Severe	High	Two of nine patients		[97]
Lacombe *et al.*	2013	Seven patients (6–19 years)	Severe	High	Five of seven patients		[113]
Authors' study	2014	12 adults	Moderate to severe	High	Six of 12 patients		
Noncontrolled studies in combination with other drugs							
Toledo *et al.*	2012	Four adults	Severe	Low	Two of four patients	With IVIG	[109]
Sánchez-Ramón *et al.*	2013	Six adults	Severe	High	Four of six patients	With rituxumab	[110]
Controlled studies							
Heil *et al.*	2010	20 adults	Moderate to severe	High	No clinical differences between the two randomized groups	13 patients in the active group	[92]
Iyengar *et al.*	2013	Eight patients (4–22 years)	Severe	High	No clinical differences between the two randomized groups	Four patients in the active group	[93]

†Doses recommended by the manufacturer adjusted by patient's weight and baseline IgE are considered high; smaller doses are considered low.
‡Patients whose SCORAD (or alternative scoring system) decreased at least to the half of the baseline measurement upon initiation of omalizumab.

treatment for AD. A recent observational, descriptive, cross-sectional, retrospective study of 61 omalizumab-responder asthma patients found that half of them developed clinical relapses after discontinuation of the drug with not all of them responding after reintroduction [118]. Other noncontrolled studies in asthma reported similar negative outcomes, even just with dose reduction [119]. Protocols in published studies of omalizumab for AD tend to use initial cycles of at least 3–4 months before measuring clinical outcomes [98–101], probably influenced by the reported reduction at this time point of free IgE and FcεRI expression in asthma patients. However, the decrease in serum IgE level does not seem to correlate with clinical response [106]. In our experience, omalizumab-responder AD patients take several weeks longer to achieve the maximum clinical benefit than asthma patients and the reduction of the dose does not affect significantly clinical outcomes. There is no parameter in the clinical routine beyond the change in the requirements of other medications for disease control, able to assess the effectiveness of omalizumab in AD patients. Patients on anti-IgE therapy should be evaluated at least every 3–6 months in order to monitor skin condition, tolerance to the drug and proper use of hygienic measures and comedication.

Published literature on omalizumab for AD does not document the evolution of patients outside the time frame of the study or after therapy discontinuation. In the article published by us, a responder patient maintained disease control up to 17 months after cessation of the therapy [113]. Taking into account the relapse-resolution nature of AD and the lower prevalence of the disease in elder subjects [1], we consider that discontinuation of omalizumab therapy in responder patients should be tried at some time point (1–2 years depending on the severity of baseline disease) after the achievement of clinical maximum benefit.

Safety of omalizumab

There is a general consensus about the overall good safety profile of omalizumab with some controlled studies reporting excellent tolerability up to 4 years. A 2009 revision of data from controlled trials concluded that incidence of anaphylaxis was 0.14% in omalizumab-treated patients and 0.07% in control subjects [120]. Of note, no serum-sickness attributable to the drug and no anti-omalizumab measurable antibodies have been reported to date [120]. Post marketing data up to 2006 estimated a slightly higher anaphylaxis rate [0.2%] attributed to omalizumab, which was in

any case in the range of the incidence for other drugs. An article from 2011 reported three patients with hypersensitivity reactions to omalizumab that required specific desensitization [121]. The rate of malignant neoplasia in omalizumab-treated patients is comparable to the one expected for studied populations [120]. Thrombocytopenia was a complication observed during animal studies that did not come up in the clinical trials. Even though some early reports related omalizumab to the appearance of Churg–Strauss syndrome in asthma patients [122], after correcting for the oral corticosteroids-sparing effect achieved by omalizumab, a causative role for the drug seems unlikely [120]. There are no reported interactions of omalizumab with other medications used for AD or other allergic diseases. As a general recommendation, omalizumab cannot be advised during pregnancy until further studies assessing safety are published. Nevertheless, indirect data from asthma clinical trials [120] favor omalizumab use in gravid women. More attention has been put over the appearance of infections in treated patients, since IgE is an important player in the host defence against parasitic helminths [81]. A randomized placebo-controlled trial in 137 adult subjects with respiratory allergy at high risk of helminth infection showed a modest increase of the incidence of parasitism in the active group [123]. Severity of infection and response to antihelminth therapy was unaltered by omalizumab [123]. However, concerns still remain and screening (and eventually treatment) before starting the therapy in patients at high risk of parasitism is recommended by the authors. Recently a severe *Echinococcus multilocularis* infection in a patient treated with omalizumab has been reported [124]. Other side effects included in the commercial label of omalizumab comprise skin mild local reactions (considered as frequents, >1%) and other less frequent (<1%) such as fatigue and cough [64]. Omalizumab did not produce any severe side effect when administered with rituximab in our study [113], but one of the patients receiving the drug together with intravenous immunoglobulin [112] developed an episode of eczema herpeticum, a severe infectious complication of AD.

Cost–effectiveness of omalizumab therapy for atopic dermatitis

The growing expenses related to the use of biological therapies have rised some concerns about the sustainability of Health Systems. However, cost–effectiveness studies of biologicals in other immune-based diseases suggest that monoclonal antibodies are cost-effective in severe cases [125]. Omalizumab is available as 75 and 150 mg prefilled syringes at prices of UK£128.07 and £256.15, respectively. A meta-analysis that included a study of the cost–effectiveness for omalizumab as an add-on therapy, compared with standard therapy alone for severe asthma in adult patients and children was published recently [126]. Authors found favorable results for omalizumab with an incremental cost–effectiveness ratio for adults of £83,822 per quality-adjusted life-year gained, and of £78,009 for children [126]. Several more limited studies on severe asthma patients provided similar conclusions and revealed that the additional cost due to the use of omalizumab was offset by the medium- and long-term savings associated with the reduction in hospital admissions and access to emergency department [127,128]. No study has been performed to date assessing the cost–effectiveness of omalizumab in responder subjects with AD. However, in our experience, most of the patients with important clinical improvements after initiation of omalizumab therapy (alone or in combination with rituximab) had a history of severe AD with repeated hospitalizations due to eczema exacerbations the years before being treated. Despite its high cost, omalizumab can be administered in the Day Care Hospital, being thus much less expensive than the costs of hospital admissions, disability, school or work absenteeism and loss of productivity.

Omalizumab effects on atopic dermatitis comorbidities

Most of the patients with severe AD phenotypes suffer from other allergic diseases such as rhinitis, asthma or food allergy. In several of the published studies patients with such comorbidities are included [129], even though the evolution of these disorders after initiation of omalizumab therapy is not always documented. In our opinion, the presence of multiple allergic diseases in the same individual might favor the prescription of anti-IgE therapy, as a mean to control the atopic diathesis in a global manner. In this regard, the ability of omalizumab to treat atopic or vernal keratoconjunctivitis (AKC and VKC respectively), uncommon but sight-threatening complications of AD [130], has been suggested. In a study from 2005, six adult patients with AKC or VKC received high doses of omalizumab during almost 2 years with four of them showing decreases in both symptom and medication scores [131]. Of note, symptoms increased in at least one patient after cessation of the therapy. In our experience, omalizumab can also treat successfully AKC in school children and interestingly, a good response of the ocular disease is not always accompanied by skin improvement.

Conclusion & final remarks

Unfortunately, conclusive evidence for a general recommendation on the use of omalizumab in AD is lacking. Even though the controlled studies published to date have not found differences with placebo, these articles

include only small number of AD individuals [95,96] and the possibility of an insufficient representation of the distinct phenotypes of the disorder cannot be completely ruled out. In this regard, one or various randomized placebo-controlled clinical trials that include sufficient number of subjects and specific analysis of the distinct disease phenotypes would be highly clarifying. Furthermore, specific matters need additional attention, including the effect and cost–effectiveness of omalizumab in patients with less severe AD phenotypes, the synergistic capacity of omalizumab when used in combination with other immunomodulators, the safety profile during pregnancy, the peculiarities of anti-IgE therapy during childhood, the effects of the discontinuation of the drug or other questions regarding the optimal doses and intervals. The future of omalizumab therapy in AD largely relies on the ability of researchers and clinicians to successfully identify the clinical and immunological features of responsiveness to specific therapies and to stratify AD patients according to their clinical and inflammatory profile. This approach would help to select subgroups of individuals that might obtain significant benefit from omalizumab. In this regard, the search for biomarkers that allow this identification will be probably continued in the next 5–10 years.

As a short summary, the authors conclude the following aspects:

- AD is an extremely complex disease with several diverse pathological mechanisms playing a role;
- The relative contribution of these disease mechanisms seems to be different in each patient/group of patients;
- It is very improbable that a drug with inhibitory effects restricted to just some arms of the immune system is going to successfully treat a significant proportion of AD patients when given in mono-therapy;
- Omalizumab does not seem effective in a majority of AD patients, but might be able to produce significant clinical improvement in subjects with high dependency on allergen sensitization. Anti-IgE therapy could provide some additional benefit in some subjects with more complex disease phenotypes when combined in synergism with other immunomodulators;
- More studies are warranted to better identify omalizumab responder patients.

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Executive summary

Background

- Atopic dermatitis (AD) is a multifactorial inflammatory disorder with Th2-driven inflammation being prevalent in the acute phase and Th1/Th17 mechanisms leading the chronic forms.
- Hygienic measures and corticosteroids are first-line therapy of AD. Sometimes oral cyclosporine is necessary. Other systemic immunosuppressors and immunomodulators show unsatisfactory profiles when used for AD therapy.

Omalizumab therapy for AD

- Omalizumab is an anti-IgE monoclonal antibody approved for the treatment of some asthma and urticaria patients that has been used in other allergic and immune-mediated diseases.
- Omalizumab binds to the Fc region of IgE competing thus with IgE specific receptors, FcεRI and CD23. Blocking IgE with omalizumab would theoretically inhibit FcεRI- and CD23-dependent cell activation.
- The effectiveness of omalizumab both in monotherapy and in combination with other drugs has been reported in several series of AD patients (including the one described by us). Controlled trials with small number of patients have not found differences with placebo. There is not conclusive evidence yet regarding the effectiveness of omalizumab for AD. However, data from published literature suggests that a beneficial effect of anti-IgE therapy might exist in cases of AD with high dependency on allergen-sensitization.

Other aspects of omalizumab therapy

- The drug displays an excellent safety and tolerability profile that was maintained up to 4 years in some studies.
- Cost–effectiveness of omalizumab in asthma patients is related to the reduction in hospital admissions and access to emergency department. Some of the AD patients that improve with omalizumab in published studies showed a history of repeated hospitalizations the years before initiation of the therapy.

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