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# IgE-Mediated Multimorbidities in Allergic Asthma and the Potential for Omalizumab Therapy



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**Allergic asthma often coexists with different pathological conditions, called multimorbidities, that are mostly of allergic nature and share a common underlying inflammatory pathophysiological mechanism. Multimorbidities of allergic asthma may influence asthma control, its severity, and patients'**

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response to treatment, and contribute to the overall socioeconomic burden of the disease. Immunoglobulin E (IgE) is known to play a central role in the pathogenesis of various allergic diseases, including asthma. Thus, IgE-mediated immunologic pathways present an attractive target for intervention in asthma and multimorbidities. In this review, we discuss the most frequently reported IgE-mediated multimorbidities in allergic asthma, including allergic rhinitis, rhinoconjunctivitis, atopic dermatitis, vernal keratoconjunctivitis, chronic rhinosinusitis with nasal polyps, food allergies, and allergic bronchopulmonary aspergillosis. Omalizumab is a recombinant humanized monoclonal antibody against IgE and has been in use to treat allergic asthma for more than a decade. We comprehensively review the clinical evidence for omalizumab in the treatment of the aforementioned multimorbidities in allergic asthma. © 2018 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;7:1418-29)

**Key words:** Omalizumab; Asthma; Multimorbidities; Treatment; Allergic rhinitis; Rhinoconjunctivitis; Chronic rhinosinusitis with nasal polyps; Vernal keratoconjunctivitis; Food allergies; Allergic bronchopulmonary aspergillosis

Allergic asthma is a chronic disease of the airways involving a complex interplay between multiple inflammatory cells and mediators.<sup>1</sup> The disease is characterized by reversible airway obstruction and airway hyperresponsiveness on exposure to aeroallergens; it is defined by immunoglobulin E (IgE) sensitization, which is clinically diagnosed based on the presence of a clinically apparent allergic reaction and an IgE response to specific aeroallergens.<sup>2</sup>

Although allergic conditions, including asthma, are frequently managed as single entities, their coexistence/co-occurrence as multimorbidities is a common phenomenon. The term multimorbidity is used to indicate the clustering and co-occurrence of diseases with a common pathological mechanism in an individual, where the primary disease is not clear.<sup>3</sup> Patients with allergic asthma very frequently also present with allergic rhinitis (AR) or rhinoconjunctivitis,<sup>4</sup> whereas patients with chronic rhinosinusitis with nasal polyps (CRSwNP) often have asthma as a multimorbidity. In children, atopic dermatitis (AD) is commonly associated with asthma.<sup>5</sup> Along with the aforementioned conditions, allergic bronchopulmonary aspergillosis (ABPA) and food allergies represent other multimorbidities.<sup>6-11</sup> Multimorbidities

*Abbreviations used*

*ABPA*- Allergic bronchopulmonary aspergillosis  
*AD*- Atopic dermatitis  
*AR*- Allergic rhinitis  
*CRS*- Chronic rhinosinusitis  
*CRSsNP*- Chronic rhinosinusitis without nasal polyps  
*CRSwNP*- Chronic rhinosinusitis with nasal polyps  
*CSU*- Chronic spontaneous urticaria  
*MeDALL*- Mechanisms of the Development of ALLergy program  
*OIT*- Oral immunotherapy  
*SE*- Staphylococcus aureus enterotoxin  
*Spl*- Staphylococcus aureus–derived serine protease–like protein  
*Th2 cells*- T-helper-2 cells  
*VKC*- Vernal keratoconjunctivitis

have been shown to contribute to poor asthma control and subsequent overtreatment of patients.<sup>12</sup> Furthermore, multimorbidities are associated with increased health care costs in patients with severe asthma.<sup>8,13</sup> In severe allergic asthma, coexisting upper airway pathological conditions present a complex multimorbidity but often share a common pathophysiological mechanism (eg, type 2 immune response) that displays considerable heterogeneity. It is known that inflammation plays an important role in the initiation and progression of multimorbidities of asthma.<sup>14</sup>

IgE has been convincingly linked to the pathophysiology of allergic asthma and other allergic conditions.<sup>15</sup> IgE-mediated allergic diseases involve multiple genetic and environmental components that interact to determine disease expression and lead to heterogeneous and frequently coexisting phenotypes.<sup>16</sup> Complex allergic diseases such as asthma, rhinitis, conjunctivitis, and food allergy may be associated with allergen-specific IgE and nonallergic mechanisms that can coexist in the same patient (termed allergic comorbidity cluster or multimorbidity) and share causal mechanisms.<sup>16,17</sup> An FP7 European Union project (No. 264357), the Mechanisms of the Development of ALLergy program (MeDALL), was initiated to identify novel mechanisms of allergy initiation during early childhood through to young adulthood. Approximately 38% of allergic multimorbidities were associated with IgE sensitization in the MeDALL study; furthermore, rather than being the sole factor for multimorbidities, IgE sensitization was suggested to be a component of a broader phenotypical presentation of patients characterized by polysensitization and multimorbidity, which was associated with the frequency, persistence, and severity of allergic symptoms.<sup>16,18</sup>

In this review, we provide an overview of the major pathological conditions with an IgE component presenting as multimorbidities with allergic asthma, and we discuss the available evidence for anti-IgE therapy with omalizumab as a viable option in the management of patients with IgE-mediated multimorbidities.

## ROLE OF IgE IN ALLERGIC PATHOPHYSIOLOGY

The mechanism of allergic asthma and the key role of IgE in its pathophysiology have been extensively studied.<sup>19,20</sup> Research has demonstrated that IgE plays a fundamental role in the triggering, development, and chronicity of the inflammatory responses within the disease.<sup>19</sup> IgE constitutes only a small fraction

of the total antibodies in human serum and has the shortest half-life in serum (approximately 2 days).<sup>21</sup> IgE binds to high-affinity FcεRI receptors expressed on the surface of mast cells and basophils and to low-affinity FcεRII receptors expressed on B cells and other hematopoietic cells, which significantly enhances the half-life of IgE.<sup>22,23</sup> IgE activity is enhanced by specific cell-surface receptor interaction, and the expression is tightly regulated in the absence of allergic disease.<sup>1,21-23</sup>

On initial allergen exposure, antigen-presenting dendritic cells sensitize naïve T cells to the allergen and direct their development into T-helper-2 (Th2) cells. This induces production of inflammatory cytokines IL-4 and IL-13 that increase FcεRII expression and trigger B cells to produce allergen-specific IgE.<sup>21,22</sup> During their class-switching to IgE-secreting plasma cells, B cells also express membrane-bound IgE, which assists in antigen processing and signal transduction. Secreted IgE binds to the FcεRI on mast cells and basophils and sensitizes them to the allergen. Repeated allergen exposure leads to cross-linking of membrane-bound IgE in mast cells and basophils, inducing cellular degranulation and the release of histamine, tryptase, cysteine-leukotrienes, and platelet-activating factors. These cytokines affect the early allergic response manifested in edema, vasodilation, and bronchoconstriction.<sup>18,23</sup> The events induced in the early response lead to the production and release of cytokines and chemokines such as IL-3, IL-4, IL-5, IL-13, CC chemokine ligand-5, and granulocyte-macrophage colony-stimulating factor, which recruit inflammatory cells such as neutrophils, eosinophils, basophils, T cells, and macrophages to the site of inflammation.<sup>18,23,24</sup> This process is known as the late allergic response, characterized by mucus hypersecretion, airway inflammation, hyperresponsiveness, and airway remodeling (Figure 1). Along with the stated role of IgE-induced inflammatory mediators, it should be noted that the activation of allergen-specific memory Th2 cells by antigen-presenting cells via IgE-facilitated allergen presentation is also key for the clinical manifestation of late allergic response.<sup>25</sup>

## COMPILATION OF LITERATURE ON ALLERGIC MULTIMORBIDITIES AND CLINICAL EVALUATION OF OMALIZUMAB

To compile relevant literature on multimorbidities to be included in this review, we conducted a literature search using the PubMed database. The search using terms “multimorbidity OR multimorbidities” and “asthma” yielded a total of 106 publications. Additional searches were carried out using the names of individual conditions, for example, “allergic rhinitis” AND “asthma.” The literature review was carried out for publication years 1999 to 2018, restricting the articles to humans and English language publications. Potentially eligible publications were manually screened and reviewed, and nonrelevant publications were excluded based on predetermined criteria such as excluding editorials, opinion pieces, articles that did not have the full text available, and articles without authors.

## IgE-MEDIATED MULTIMORBIDITIES AND THE EFFECT OF OMALIZUMAB

More than 70% of symptomatic patients with allergy (having at least 1 positive skin prick test or at least 1 specific IgE > 0.35 kU/L) may be sensitized and clinically allergic to either 1 (monosensitization) or more allergens (polysensitization).<sup>15</sup> de Jong

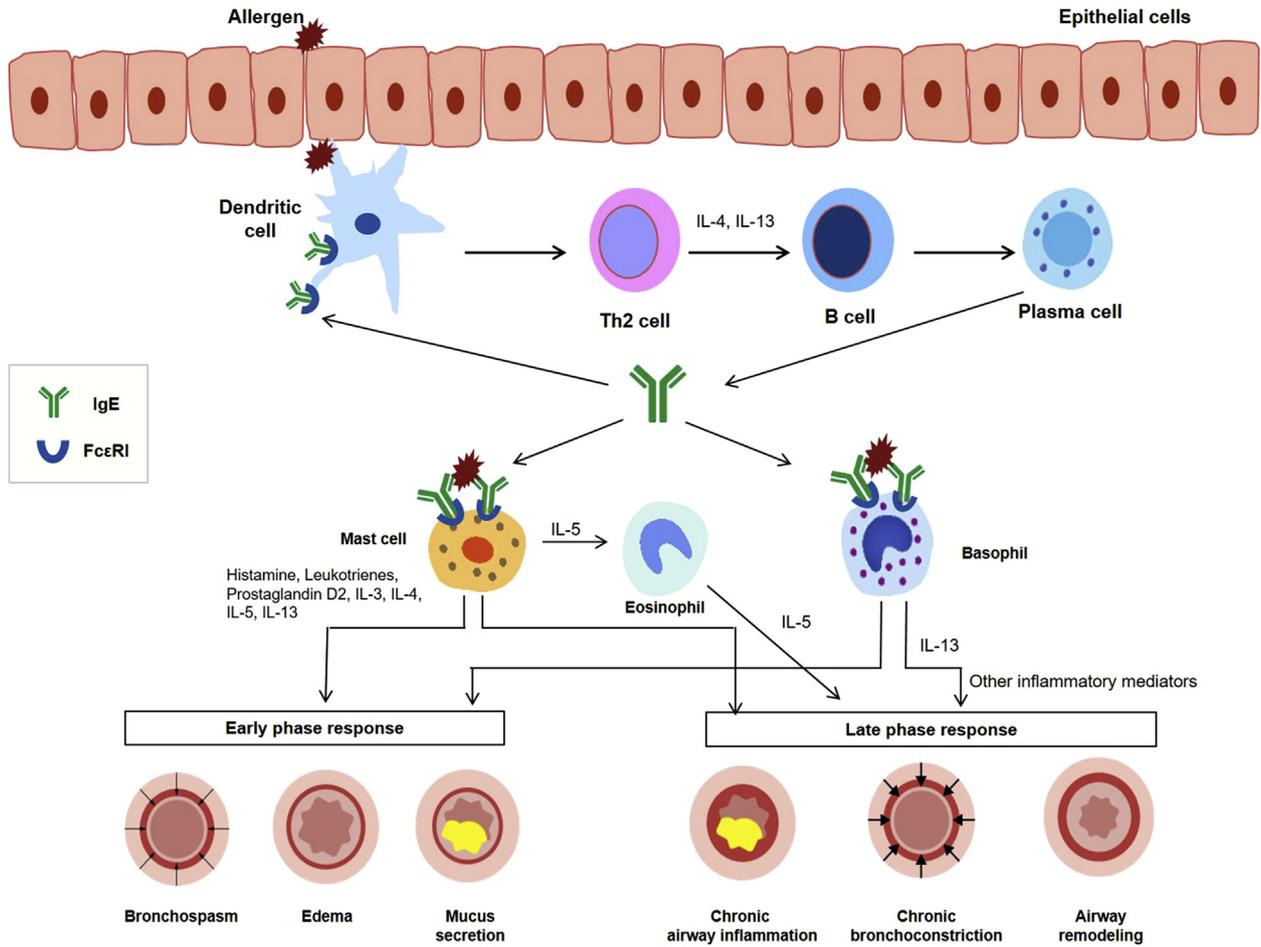


FIGURE 1. Immunological mechanisms in IgE-mediated allergic diseases. *Th2 cell*, T-helper-2 cell.

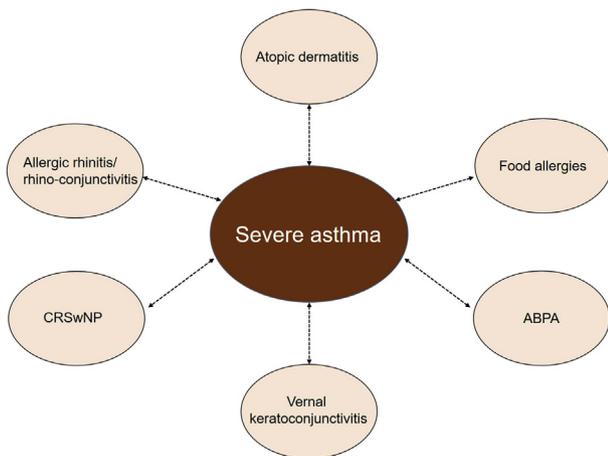


FIGURE 2. Multimorbidities associated with severe allergic asthma. *ABPA*, Allergic bronchopulmonary aspergillosis; *CRSwNP*, chronic rhinosinusitis with nasal polyps.

et al<sup>26</sup> proposed to use the term “paucisensitization” to describe 2 to 4 sensitizations and “polysensitization” to describe 5 or more sensitizations. Polysensitization can be categorized into: (1) cross-reactivity/cross-sensitization, which is the same IgE binding to several different allergens with common structural features; and (2) cosensitization, which is the simultaneous presence of different IgEs that bind to allergens that may not necessarily have common structural features.<sup>27</sup> Important clinical and immunological differences exist between patients who are mono- and polysensitized, which indicates that polysensitization is the expression of a distinct disease in both children and adults. Persistence of allergic diseases over time is associated with multimorbidity and/or allergic polysensitization; moreover, polysensitization was shown to be higher in patients with multimorbidity in comparison with those with a single allergic disease.<sup>15</sup>

Some studies in allergic asthma have shown that multimorbidities are independent predictors of key asthma outcomes.<sup>28</sup> Therefore, the choice of treatment in patients with severe asthma should be optimized based on any existing multimorbidities as these may define the asthma phenotype and

**TABLE I.** Efficacy of omalizumab in patients with allergic rhinitis/rhinoconjunctivitis

Study	Design	No. of patients	Primary (or coprimary) endpoint	Primary outcome
Adelroth et al <sup>44</sup>	A randomized, double-blind, placebo-controlled, parallel-group study	251	Average daily nasal symptom severity score (sneezing, itching, runny, and stuffy nose) from diary data collected over the double-blind treatment period	Significant between-treatment differences ( $P < .001$ ) in favor of omalizumab were observed in average daily nasal symptom severity scores
Casale et al <sup>45</sup>	A randomized, double-blind, placebo-controlled, multicenter, dose-ranging study	536	The average daily nasal symptom severity score	Average nasal symptom severity and duration scores over the entire pollen season were consistently and significantly lower in the omalizumab 300 mg group vs the placebo group ( $P = .002$ ). During the severe pollen season, average nasal symptom severity scores were also significantly lower in the 300 mg ( $P = .001$ ) and 150 mg ( $P = .01$ ) omalizumab groups than in the placebo group
Chervinsky et al <sup>46</sup>	A randomized, double-blind, phase 3 study	289	Mean daily nasal severity score (as determined from patient daily diary cards) during 16 wk of treatment	During 16 wk of treatment, the mean daily nasal severity score was significantly lower in omalizumab-treated patients compared with placebo ( $P < .001$ )
Vignola et al <sup>47</sup>	A multicenter, randomized, double-blind, parallel-group, placebo-controlled study	405	Incidence of asthma exacerbations during the 28-wk treatment period and the proportion of patients with improvement in both asthma and rhinitis QoL scores	Fewer patients treated with omalizumab experienced asthma exacerbations (20.6%) than placebo-treated patients (30.1%; $P = .02$ ). A clinically significant ( $\geq 1.0$ point) improvement in both asthma QoL questionnaire and rhinitis QoL questionnaire was seen in 57.7% of omalizumab patients compared with 40.6% of placebo patients ( $P < .001$ )
Masieri et al <sup>48</sup>	A longitudinal study	11	General clinical conditions and intensity of individual symptoms (nasal obstruction, rhinorrhea, itching, sneezing, tearing) using the visual analog scale (VAS; 1 = no symptoms, to 10 = worst possible symptoms)	VAS scores for general symptomatology ( $P = .0125$ ) and symptoms including nasal obstruction ( $P = .005$ ), rhinorrhea ( $P = .007$ ), itching ( $P = .041$ ), and sneezing ( $P < .003$ ) were significantly reduced with omalizumab compared with baseline
Kopp et al <sup>49</sup>	A randomized, double-blind, placebo-controlled, multicenter study	130	Superiority of depigmented specific immunotherapy (SIT) in combination with omalizumab compared with depigmented SIT monotherapy for daily symptom load averaged over the pollen season of the core study	Combination therapy of SIT with omalizumab reduced the symptom load by 39% ( $P = .0464$ ) over SIT monotherapy. This difference was mainly due to reduced symptom severity ( $P = .0044$ )

QoL, Quality of life.

consequently could affect asthma treatment outcomes.<sup>29</sup> Indeed, the American Thoracic Society/European Respiratory Society guidelines now recognize the identification of multimorbidities as an essential part of treating severe asthma.<sup>30</sup> Therefore, the management of multimorbidities is central to the systematic approach to overall asthma control.<sup>28-31</sup> The multimorbidities in asthma discussed in this review are AR/rhinoconjunctivitis, vernal keratoconjunctivitis (VKC), AD, CRSwNP, food allergies, and ABPA (Figure 2).

### Allergic rhinitis and rhinoconjunctivitis

AR is a symptomatic disorder of the nasal mucus membranes after allergen exposure, characterized by IgE-mediated inflammation of these membranes.<sup>32</sup> Compelling evidence exists for the overlap between AR and asthma.<sup>33,34</sup> AR and asthma are characterized by a similar inflammatory response as the upper and lower airways have a similar cellular structure of ciliated, pseudostratified columnar epithelium with goblet cells; nevertheless, it should be noted that differences do exist in the extent of tissue remodeling between the

**TABLE II.** Efficacy of omalizumab in patients with asthma and vernal keratoconjunctivitis

Study	Design	No. of patients	Primary (or coprimary) endpoint	Primary outcome
Sánchez et al <sup>53</sup>	Case study	1	Clinical effect of omalizumab in a patient with severe vernal keratoconjunctivitis coexistent with asthma	After 6 wk of omalizumab therapy, the patient presented clinically important improvement in ocular symptoms
de klerk et al <sup>54</sup>	Case study	1	Clinical effect of omalizumab in a patient with severe vernal keratoconjunctivitis coexistent with asthma	Signs and symptoms of vernal keratoconjunctivitis resolved completely with monthly subcutaneous omalizumab treatment
Doan et al <sup>55</sup>	Retrospective review of case studies	4	Clinical effect of omalizumab in patients with severe vernal keratoconjunctivitis coexistent with asthma	Three patients responded to omalizumab treatment, with a decrease in global symptoms (median symptom rating decreasing from 89 to 29 on a 100-mm visual analog scale), frequency and in duration of the inflammatory flares, and also a decreased need for topical steroid
Occasi et al <sup>56</sup>	Case study	1	Clinical effect of omalizumab in a patient with vernal keratoconjunctivitis coexistent with uncontrolled asthma	After 3 mo of treatment with omalizumab, asthma control was reached a complete resolution of vernal keratoconjunctivitis

**TABLE III.** Efficacy of omalizumab in patients with chronic rhinosinusitis

Study	Design	No. of patients	Primary (or coprimary) endpoint	Primary outcome
Gevaert et al <sup>71</sup>	A randomized, double-blind, placebo-controlled study	24	The difference in total nasal endoscopic polyp scores compared with baseline after 16 wk of treatment	There was a significant decrease in total nasal endoscopic polyp scores after 16 wk in the omalizumab-treated group ( $-2.67$ , $P = .001$ ) compared with baseline
Vennera Mdel et al <sup>72</sup>	Case studies	19	The size of NP scored in both nasal cavities using nasal endoscopy. Scored as 0 (no polyp), 1 (polyps restricted to the middle meatus), 2 (polyps in the middle meatus but not reaching the upper edge of the inferior turbinate), 3 (polyps between the upper and lower edges of the inferior turbinate), and 4 (large polyps reaching the floor of the nasal fossa), with a bilateral total score ranging from 0 to 8	NP size was significantly reduced at the end of follow-up vs baseline ( $P = .035$ ). No patient needed additional surgery during omalizumab treatment
Penn and Mikula <sup>73</sup>	A retrospective study	8	Effect of omalizumab on recurrence of nasal polyps after endoscopic sinus surgery using sinus computed tomography and nasal endoscopic examination	The nasal polyp scores significantly improved in the omalizumab-treated patients than in the preoperative group

NP, Nasal polyps.

nose (in AR) and bronchi (in asthma).<sup>34,35</sup> Several epidemiologic studies have provided strong evidence for the association of the development of asthma with a previous history of either seasonal or perennial AR.<sup>36,37</sup> Large worldwide studies such as The International Study of Asthma and Allergies in Childhood epidemiological research program conducted between 2002 and 2003 showed that the prevalence of asthma, AR, allergic rhinoconjunctivitis, and other allergic diseases had risen when compared with 5 years before the

study.<sup>38</sup> Previous epidemiological studies have reported that up to 40% of patients with AR also developed asthma and up to 80% of patients with asthma reported having AR.<sup>33,39,40</sup> In a recent study, the coexistence of asthma and AR was found to be the most common allergic multimorbidity,<sup>41</sup> supporting the “one airway, one disease” hypothesis and common epidemiologic, pathologic, and physiologic characteristics, and a common therapeutic approach for both rhinitis and asthma.<sup>42</sup> The association of rhinoconjunctivitis and asthma

**TABLE IV.** Efficacy of omalizumab in patients with atopic dermatitis

Study	Design	No. of patients	Primary (or coprimary) endpoint	Primary outcome
Iyengar et al <sup>78</sup>	Randomized, placebo-controlled study	8	Levels of thymic stromal lymphopoietin (TSLP), thymus and activation-regulated chemokine (TARC), OX40 ligand (OX40L), and other cytokines involved in atopic dermatitis (AD) measured by using cytometric bead arrays; Scoring Atopic Dermatitis (SCORAD) scores	All patients receiving omalizumab had substantially decreased levels of TSLP, OX40L, TARC (involved in T-helper-2 polarization) and IL-9 compared with placebo. Patients who received omalizumab showed SCORAD score reductions of approximately 20% to 50%
Heil et al <sup>79</sup>	An explorative single center, randomized, placebo-controlled, double-blind mechanistic study	20	Effect of omalizumab on immunological disease parameters assessed throughout the study: flow cytometry, immunohistology, and the measurement of serum IgE levels	Omalizumab: (1) reduced free serum IgE, (2) lowered surface IgE and FcεRI expression on different peripheral blood mononuclear cells, (3) reduced the saturation of FcεRI with IgE, (4) increased the number of free FcεRI, and (5) lowered the number of IgE+, but not of FcεRI+ cells in skin
Sheinkopf et al <sup>82</sup>	Prospective analysis of treatment efficacy	21	AD severity at 0, 1, 3, 6, and 9 mo via an Investigator Global Assessment index based on a modified SCORAD index	All patients showed clinical and statistically significant improvement of their atopic dermatitis from month 0 to months 1, 3, 6, and 9 on treatment with omalizumab

symptoms was shown to be frequent and associated with more severe asthma symptoms in patients with concomitant AR.<sup>43</sup>

**Clinical evaluation of omalizumab.** Both randomized-controlled and observational-type clinical studies have demonstrated the effectiveness and safety of omalizumab in patients with AR. The study populations included patients with a history of seasonal or perennial AR as well as those with seasonal AR and concomitant severe asthma. In these studies, omalizumab provided improvement in symptoms, as indicated by significantly lower symptom scores on treatment, reduction in concomitant and rescue medication use, improved quality of life, decreased IgE levels, and reduction in asthma exacerbations. The findings from a few key relevant clinical studies are presented in [Table I](#).

**Vernal keratoconjunctivitis**

VKC is a chronic relapsing allergic eye disease with immediate and delayed hypersensitivity reactions (both IgE and non-IgE mediated) that can result in significant visual loss.<sup>50</sup> Conventional therapy for allergic conjunctivitis is generally not adequate for VKC;<sup>51</sup> in a large retrospective study, almost 85% of patients with VKC required treatment with topical corticosteroids at some point during follow-up.<sup>52</sup>

**Clinical evaluation of omalizumab.** A few reports have shown promising results of omalizumab in the treatment in both adults and children with VKC coexisting with asthma, without the excessive adverse effects associated with topical corticosteroid therapy. It should be noted that these findings are mostly from case studies and thus are from a very small patient population. Therefore, controlled studies in a larger number of patients are required to determine the treatment regimen with omalizumab in patients with VKC. We have

presented the findings from a few key relevant case studies in [Table II](#).

**Chronic rhinosinusitis**

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) or without (CRSSNP) involves long-term inflammation of the paranasal sinus mucosa for a minimum of 12 weeks; specifically in CRSwNP, patients may suffer with the condition for decades.<sup>57,58</sup> Patients with CRSwNP are especially prone to develop asthma and show an incidence of asthma of 20% to 70% dependent on the degree of type 2 inflammation in the polyp mucosa.<sup>59</sup> CRSwNP is prevalent in 4% of the asthmatic patients and around 15% of nonatopic asthmatic patients; however, these figures may be higher when patients are thoroughly investigated, including nasal endoscopy.<sup>17</sup> It is important to note that the conventional phenotyping of CRS into CRSwNP and CRSSNP might not adequately reflect the pathophysiological variety among patients with CRS; in this regard, distinct inflammatory endotypes have been identified within patients with CRS, which largely correlated with phenotypes and further differentiated the phenotypes.<sup>59</sup> The GA<sup>2</sup>LEN study showed that there is a very strong association of CRS with asthma; almost 40% of patients with asthma suffered from comorbid CRS.<sup>60</sup> Higher levels of sputum and serum eosinophils, and exhaled nitric oxide levels, in patients with CRS suggest that it is closely related to lower airway inflammation in severe asthma.<sup>61</sup> CRSwNP is associated with local immunoglobulin hyperproduction and the presence of IgE antibodies against *Staphylococcus aureus* enterotoxins (SEs), also called staphylococcal superantigens.<sup>62</sup> This is in line with the evidence that both CRSwNP and asthma show increased nasal *S. aureus* colonization.<sup>63-65</sup> *S. aureus*-derived serine protease-like protein (Spl) D and other proteases secreted by *S. aureus* have recently been identified as inducers of allergic

**TABLE V.** Efficacy of omalizumab in patients with food allergies

Study	Design	No. of patients	Primary (or coprimary) endpoint	Primary outcome
Andorf et al <sup>92</sup>	A blinded, phase 2, randomized, controlled study	48	Proportion of patients who passed double-blind, placebo-controlled food challenges to at least 2 of their offending foods at week 36	At week 36, a significantly greater proportion of the omalizumab-treated (30 [83%] of 36) vs placebo (4 [33%] of 12) participants passed double-blind, placebo-controlled food challenges to 2 or more of their offending foods (odds ratio: 10.0, 95% CI 1.8-58.3, $P = .0044$ )
Rafi et al <sup>96</sup>	A prospective pilot study	22	Symptoms and severity of allergic reaction before and after omalizumab treatment for 1-y duration	All patients displayed significant improvement as shown by a decrease/lack of symptoms on re-exposure to sensitized foods. Clinical improvement by the sixth dosage of omalizumab (150-300 mg every 2-4 wk) was noted by history and physical examination
Sampson et al <sup>97</sup>	A phase 2, randomized, double-blind, parallel-group, placebo-controlled study	14	Tolerability to peanut in allergic patients	Omalizumab increased the tolerability to peanut: 4 (44.4%) omalizumab-treated subjects vs 1 (20%) placebo-treated subject could tolerate >1000 mg peanut flour during an oral food challenge after 24 wk of treatment with study drug ( $P = .324$ )
Wood et al <sup>99</sup>	A double-blind, placebo-controlled study	57	Sustained unresponsiveness, defined as the absence of dose-limiting symptoms in both month 28 and month 32 oral food challenges, ie, sustained unresponsiveness measured after 8 wk off of milk oral immunotherapy in patients treated with omalizumab vs placebo	At month 28, a total of 24 (88.9%) omalizumab-treated patients and 20 (71.4%) placebo-treated patients passed the "desensitization" oral food challenge ( $P = .18$ ). At month 32, sustained unresponsiveness was observed in 48.1% in the omalizumab group and 35.7% in the placebo group ( $P = .42$ )
Schneider et al <sup>100</sup>	Desensitization study	13	Rate of desensitization to peanut allergy	After pretreatment with omalizumab, all patients tolerated the initial 11 desensitization doses given on the first day, including the maximum dose of 500 mg peanut flour, requiring minimal or no rescue therapy
MacGinnitie et al <sup>101</sup>	Desensitization study	37	Rate of desensitization to peanut allergy	The median peanut dose tolerated on the initial desensitization day was 250 mg for omalizumab-treated patients vs 22.5 mg for placebo-treated patients. Twenty-three patients receiving omalizumab vs 1 patient receiving placebo passed the 4000 mg food challenge

CI, Confidence interval.

asthma.<sup>66</sup> The Spls act as allergens and superallergens, shifting the immune reaction further into type 2 inflammation.<sup>54,66</sup> The presence of both the enterotoxins and the Spls has been demonstrated in the upper airway mucosa using proteomics.<sup>67</sup> Studies have shown the presence of polyclonal-specific IgE, including IgE to SEs, a high total IgE level, and a high prevalence of asthma in patients with NP;<sup>68</sup> it has been postulated that mucosal polyclonal IgE contribute to persistent inflammation by

continuously activating mast cells in patients with NP.<sup>69</sup> IgE to SEs can be measured in serum, and SE-induced IgE levels have been shown to be a risk factor for asthma severity.<sup>65,70</sup> In addition, increased levels of total IgE were predictive of asthma comorbidity in patients with CRSwNP.<sup>66</sup>

**Clinical evaluation of omalizumab.** Omalizumab was found to be effective in reducing the severity of nasal polyps in

**TABLE VI.** Efficacy of omalizumab in patients with allergic bronchopulmonary aspergillosis

Study	Design	No. of patients	Primary (or coprimary) endpoint	Primary outcome
Aydın et al <sup>107</sup>	A retrospective chart review	14	Lung function, asthma control test score, mean oral corticosteroid usage, asthma exacerbations, hospitalization	Treatment with omalizumab resulted in: (1) significant increase in FEV <sub>1</sub> from baseline ( $P = .02$ ); (2) increase in mean asthma control test score at all time points compared with the basal score ( $P = .001$ ); (3) significantly decreased mean oral corticosteroid dosage ( $P = .001$ ); and (4) zero exacerbation and hospitalization rate at the final assessment. Eleven of the patients (78.6%) responded perfectly to omalizumab
Voskamp et al <sup>108</sup>	A randomized, double-blind, placebo-controlled, cross-over study	13	Number of exacerbations	Rate of exacerbations decreased significantly in the active treatment phase compared with the placebo phase (2 vs 12 events, $P = .048$ )

FEV<sub>1</sub>, Forced expiratory volume in 1 s.

patients with coexisting severe asthma. We have presented the outcomes of a few key relevant clinical studies in Table III. It should be noted that the evidence presented here is mainly from noncontrolled and case studies, which included a low number of patients; in this regard, larger controlled clinical trials would be needed to determine the generalized efficacy and regimen of omalizumab in these patients. Currently, the effectiveness of omalizumab in nasal polyps (with or without concurrent asthma) is being explored in 2 ongoing phase 3 randomized clinical trials (Clinicaltrials.gov: NCT03280550, NCT03280537).

### Atopic dermatitis

AD, AR, and asthma are said to form the triad of atopic diseases. AD is one of the most common allergic skin disorders found in children. The prevalence of AD is up to 24% in developed countries, and has risen in recent years together with an increased prevalence of asthma, representing a major burden on health care cost.<sup>74,75</sup> AD is frequently associated with elevated serum IgE levels in individuals with a history of allergies and respiratory symptoms such as AR and allergic asthma.<sup>17</sup> The epidermal and dermal dendritic cells both express high-affinity FcεRI receptors on their cell surface. It has been estimated that approximately one-third of young patients with AD develop asthma.<sup>76</sup> Moreover, a significant relationship has been demonstrated between the severity of AD and bronchial asthma, and the duration of the skin lesions.<sup>77</sup>

**Clinical evaluation of omalizumab.** Overall, omalizumab was not markedly effective in treating AD in patients with asthma<sup>78-82</sup> (Table IV). Moreover, recommendation for its use in clinical practice for patients with AD awaits evidence from larger randomized controlled trials.<sup>80</sup> The Atopic Dermatitis Anti-IgE Paediatric Trial is one such randomized study that will assess whether omalizumab improves AD compared with placebo in patients with coexisting asthma.<sup>81</sup>

### Food allergies

Food allergies are immune-mediated adverse reactions to various foods that may involve IgE-mediated immediate hypersensitivity reactions, delayed non-IgE-mediated reactions, or contributions from both IgE-mediated and non-IgE-mediated

immune pathways.<sup>83</sup> Most commonly encountered food allergens include milk, eggs, tree nuts, peanuts, soy, wheat, fish, and shellfish. IgE-mediated food allergy can affect all ages, impacts quality of life, and can lead to very severe—even fatal—reactions as well as cross-reactive IgE responses to inhalant allergens.<sup>84</sup> Overall, the prevalence of food allergies ranges from less than 0.2% to more than 10%; the prevalence is influenced by factors including age (eg, egg and milk are major allergens in children but disappear later in life) and geographical location.<sup>85</sup> An EU-funded integrated project (EuroPrevall) was conducted to provide a framework for identification of risk factors and management of food allergies by examining the complex interactions between food intake and metabolism, immune system, genetic background, and socioeconomic factors.<sup>86</sup> In the INCO EuroPrevall study, probable food allergy was defined as self-reporting of adverse symptoms after the consumption of food and a specific IgE level of  $\geq 0.35$  kU/L to the same food.<sup>87</sup> Children suffering from coexisting food allergies and asthma were at increased risk of severe anaphylaxis, which can be fatal, particularly if their asthma was uncontrolled.<sup>88</sup> Although it is known that allergic reactions to food can trigger lower respiratory symptoms and asthma, food allergy generally does not present with chronic or isolated respiratory symptoms.<sup>88</sup>

**Clinical evaluation of omalizumab.** Oral immunotherapy (OIT) is more effective than other routes in the treatment of food allergies, but safety has been a major limitation due to the risk of adverse reactions.<sup>89</sup> To improve the safety profile of OIT and maintain or increase its efficacy, adjuvant therapy with omalizumab has been explored in several trials in severe peanut allergy, milk allergy, egg allergy, and multiple food allergy, with significant clinical improvement in both adults and children.<sup>90-92</sup> Recent evidence has suggested that the concomitant use of omalizumab with OIT can improve OIT protocols and outcomes in patients with food allergies.<sup>93-96</sup> This effect correlated with the effect of omalizumab on basophil reactivity, which may play a vital role in the early events of allergic response to food.<sup>94-96</sup> In addition, several studies have assessed the effect of anti-IgE monotherapy in patients with food allergy. In a phase 2 study, omalizumab was shown to significantly increase the

tolerability of allergic patients to peanut compared with placebo on oral food challenge, although this study was stopped early.<sup>97</sup> A placebo-controlled study that evaluated the efficacy of anti-IgE monotherapy (with talizumab) in patients with peanut allergy showed that the threshold of sensitivity to peanut on oral food challenge was significantly increased with this therapy.<sup>98</sup> Table V describes the details of key clinical studies that evaluated the efficacy of omalizumab in patients with food allergy.

### Allergic bronchopulmonary aspergillosis

ABPA is an allergic pulmonary disorder caused by hypersensitivity to the fungus *Aspergillus* species (most commonly *Aspergillus fumigatus*). ABPA is also sometimes classified as a distinct endotype of asthma based on its specific pathophysiological mechanisms. Globally, it has been reported that over 4.8 million patients with asthma have ABPA; however, the exact prevalence of this disease is still unknown.<sup>102</sup> According to the International Society for Human and Animal Mycology working group, the prevalence of aspergillus sensitization in patients with asthma ranged from 5.5% to 38.5%, and the prevalence of ABPA varied between 2.5% and 22.3%, with a pooled prevalence of 8.4% in asthma.<sup>103</sup> The fungal antigens from *A. fumigatus* cause a type I (IgE-mediated) reaction that is responsible for presentation of ABPA. Type III (IgG-mediated immune complex) and type IV (cell-mediated) responses have also been implicated, but tissue invasion does not occur. Therefore, the total IgE levels are generally high in ABPA.<sup>104,105</sup>

**Clinical evaluation of omalizumab.** A systematic review of 102 cases from 30 publications showed that treatment with omalizumab reduced serum free IgE levels in patients with ABPA, especially in those with a baseline IgE level of >1000 IU/mL, and also reduced asthma exacerbations, thus showing potential benefits in severe ABPA.<sup>106</sup> In addition, retrospective analysis of case studies and randomized studies have demonstrated that omalizumab improved asthma symptoms and lung function in patients with asthma and ABPA<sup>107,108</sup> (Table VI). However, larger randomized, double-blind, placebo-controlled trials are required to establish the effectiveness of omalizumab in this patient population.<sup>106</sup>

### SUMMARY AND CONCLUSIONS

The important role of IgE in mediating allergic reactions is well established and best corroborated by the clinical benefits of the anti-IgE monoclonal antibody omalizumab in allergic diseases.<sup>109,110</sup> Similar to coexisting conditions in other diseases, IgE-mediated multimorbidities in patients with allergic asthma contribute to the lack of disease control and impose a considerable burden on patients, caregivers, and health care systems.<sup>111</sup> Because IgE is involved in pathologies distinct from or overlapping with those of asthma, anti-IgE therapy is approved for chronic spontaneous urticaria (CSU) and is currently being assessed in conditions such as AR, CRSwNP, AD, and food allergies.<sup>109</sup> Indeed, targeting IgE has proved to be a successful approach to allergic diseases that have poor responses to conventional treatments. Although the approved indications for omalizumab are currently limited to allergic asthma and CSU, its potential in the treatment of other allergic multimorbidities is becoming increasingly apparent.<sup>111</sup> Evidence suggests that the treatment of allergic asthma with omalizumab not only results in improvements in asthma symptoms but also frequently improves

outcomes of any coexisting conditions.<sup>112,113</sup> A retrospective, observational study that assessed the efficacy of omalizumab in patients with asthma and other concomitant allergic diseases such as rhinosinusitis, AD, and ABPA showed improvement in symptoms of these allergic diseases, suggesting that omalizumab has a role in allergic disease beyond its current use.<sup>114</sup> Even beyond diseases with an atopy component, omalizumab reduced bronchial mucosal IgE+ mast cells, downregulated FcεRI expression, and improved lung function despite withdrawal of conventional therapy in nonatopic asthmatics.<sup>115,116</sup>

In spite of common components in their pathogenesis, allergic diseases are still viewed as independent conditions. Although the nature of the association among different allergic diseases is still under investigation, it is acknowledged that they tend to cluster and patients may present with concomitant or consecutive diseases, that is, allergic multimorbidities. Studies that will assess the relationship between coexisting diseases in groups of patients with different allergic sensitizations will provide important insights into the impact of multimorbidities. Furthermore, despite the growing evidence for the application of anti-IgE therapy in IgE-mediated multimorbidities of allergic asthma, larger and well-designed clinical studies may further confirm the efficacy and safety of the use of omalizumab. It should be noted that because patients with allergic multimorbidities may exhibit higher levels of IgE than those indicated in the dosing table for asthma, the dosages of anti-IgE treatments would need to be adjusted to achieve optimal efficacy in treating these conditions. Future research may provide a better understanding of the interplay between multimorbidities and allergic asthma, thus helping to identify targeted treatments and improve clinical outcomes in these coexisting allergic diseases.

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