

## Review Articles

## Potential benefit of omalizumab in respiratory diseases



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## ABSTRACT

**Objective:** To provide an overview of primary and secondary mechanisms associated with anti-IgE therapy and their relation to other potential indications in diseases affecting the respiratory tract.

**Data Sources:** Literature from PubMed searches for publications providing insight into secondary mechanisms resulting from anti-IgE therapy and publications reporting on the use of omalizumab to treat conditions that affect the respiratory tract, other than severe atopic asthma.

**Study Selections:** Clinical trials or case reports were identified for asthma in patients without atopy, allergic rhinitis, nasal polyposis, and allergic bronchopulmonary aspergillosis.

**Results:** There is substantial evidence from controlled trials supporting a benefit for allergic rhinitis. Case reports and series on more than 50 patients with allergic bronchopulmonary aspergillosis have been published, including patients with or without cystic fibrosis; most have reported benefits in terms of decreased steroid use, exacerbation rates, and, in patients with cystic fibrosis, improvement in lung function. Several small controlled studies on nasal polyposis have shown equivocal results. One small controlled trial in patients with nonatopic asthma showed a significant improvement for lung function but not in exacerbation rate or asthma scores.

**Conclusion:** Recent insight into the immunopathology of respiratory diseases should be used to identify patient populations likely to respond to anti-IgE therapy. Controlled clinical trials are needed to confirm efficacy and determine the clinical significance of the effects of omalizumab in these populations.

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## Introduction

Allergic reactions involve a complex cascade of cellular and humoral factors, many of which are under investigation as targets for therapeutic antibodies, and promising new tools for manipulating the immune system are emerging.<sup>1</sup> Elevated levels of IgE are associated with different respiratory conditions, including allergic asthma, allergic rhinitis, nasal polyposis (NP), and bronchopulmonary aspergillosis. Omalizumab is currently the only biologic approved for treatment of severe atopic asthma. The authors evaluated the

evidence supporting the use of omalizumab in respiratory conditions other than severe allergic asthma in light of its mechanism of action.

## Omalizumab

Omalizumab is a recombinant humanized monoclonal IgG antibody that selectively binds the Cε3 domain of free IgE heavy chains and greatly decreases levels of free IgE. The Cε3 domain is masked on receptor-bound IgE; thus, omalizumab cannot trigger effector cell degranulation. The central role that IgE plays in allergic inflammation provides a strong rationale for the use of anti-IgE therapy in patients with severe persistent allergic asthma.<sup>2,3</sup> Numerous randomized controlled trials have reported the efficacy of omalizumab in severe asthma not controlled by optimal therapy with inhaled corticosteroids and long-acting β<sub>2</sub>-agonists.<sup>4,5</sup> Aggregated safety data from more than 7,500 patients from 17 randomized trials and postmarketing surveillance have indicated that omalizumab has a favorable safety and tolerability profile.<sup>6</sup>

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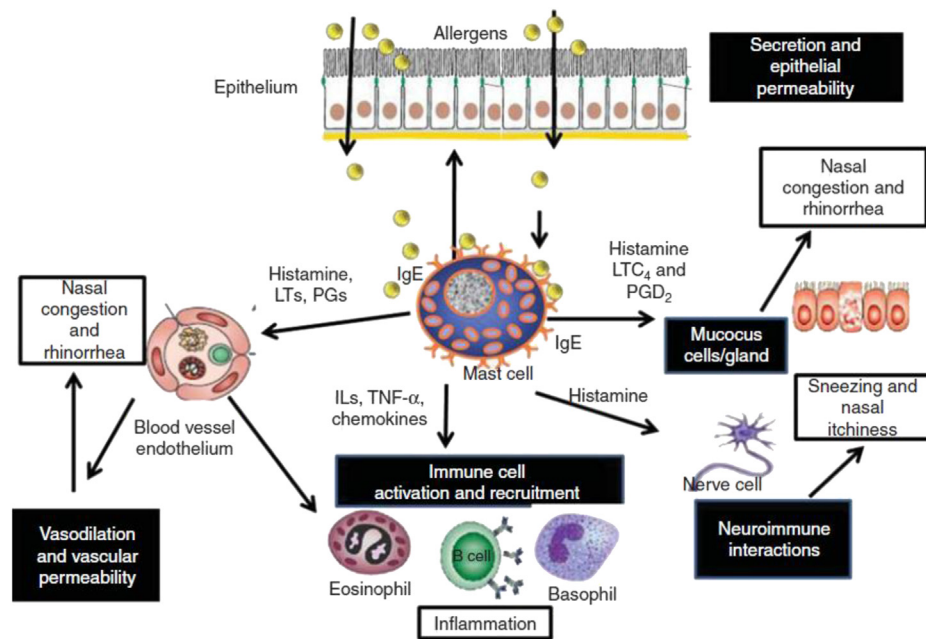


**Figure 1.** Pathophysiological mechanisms of allergic rhinitis. IL<sub>8</sub>, interleukin-8; LTC<sub>4</sub>, leukotriene C<sub>4</sub>; LTs, leukotrienes; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; PGs, prostaglandins; TNF-α, tumor necrosis factor-α. Reproduced with permission by Informa Healthcare from Vashisht P, Casale T. Omalizumab for treatment of allergic rhinitis. *Expert Opin Biol Ther*. 2013; 13:933–945. Copyright © 2013, Informa Healthcare.

### Mechanisms

Immunoglobulin E is best known for its role in mast cell sensitization and degranulation in immediate hypersensitivity reactions. Anti-IgE therapy lowers levels of IgE and prevents binding to IgE receptors, thereby attenuating early- and late-phase reactions.<sup>7</sup> The ability of omalizumab to prevent mast cell and basophil degranulation represents its primary mechanism of action and provides significant improvement in asthma control in terms of exacerbation rates and severity of respiratory symptoms.

Lowering free IgE levels has some secondary effects that may decrease inflammation and exacerbations in sensitized individuals and may prevent further sensitization through effects on antigen-presenting cells (APCs). The level of free IgE regulates the number of FcεRI receptors on cells by binding and retaining receptors at the cell surface, preventing receptor internalization and degradation.<sup>8</sup> Omalizumab treatment decreases FcεRI levels on basophils and mast cells and thus decreases their responsiveness to antigen challenge.

In addition to blocking activation of effector cells by lowering levels of the αβγ<sub>2</sub> form of FcεRI on their surfaces, omalizumab could influence sensitization by decreasing the expression of the αγ<sub>2</sub> form of FcεRI expressed on APCs.<sup>9,10</sup> Dendritic cells (DCs) are the most potent APCs, with the capacity to activate memory T cells and naive T cells. IgE binding on APCs enhances presentation of IgE-reactive antigens to allergen-specific T cells, driving an inflammatory T-helper cell type 2 (T<sub>H</sub>2) response.<sup>11</sup> This implies that anti-IgE therapy could decrease the numbers of allergen-specific T<sub>H</sub>2 cells by inhibiting expansion and differentiation of naive allergen-specific T cells into T<sub>H</sub>2 cells and decrease inflammatory cytokines by decreasing T<sub>H</sub>2 cell activation. Antigen presentation by DCs is decreased in patients receiving omalizumab.<sup>9</sup> Decreases in allergen-induced T-cell proliferation and T<sub>H</sub>2 cytokine secretion correlate with receptor downregulation. Airway DCs are more numerous in patients with asthma and are significantly decreased by anti-IgE treatment.<sup>12</sup> Thus, sustained blockade of IgE with omalizumab may reverse the T<sub>H</sub>2 polarization of the immune response in allergic asthma and other T<sub>H</sub>2-driven inflammatory diseases.

Basophils traffic to the airway mucosa in patients with atopic asthma and produce T<sub>H</sub>2 cytokines (interleukin [IL]-4 and IL-13) that may serve as an early source of T<sub>H</sub>2 cytokines in the initial phases of allergen sensitization.<sup>13</sup> IL-4 production by basophils can be triggered in response to IL-33, a recently described type-2–initiating cytokine in the IL-1 family that is released from damaged epithelial cells.<sup>14</sup> Omalizumab therapy decreases the anti-IgE stimulated ex vivo production of IL-4, IL-8, and IL-13 by basophils in patients with asthma,<sup>15</sup> but paradoxically increases sensitivity of basophils to ex vivo stimulation by IgE crosslinking.<sup>16</sup>

Omalizumab also may decrease IgE production by B cells through an effect on the low-affinity IgE receptor (FcεRII, CD23), which functions in IgE homeostasis.<sup>17</sup> This mechanism has been invoked as an explanation for the efficacy of omalizumab in patients with very high levels of total IgE.<sup>18</sup>

### Omalizumab in Respiratory Conditions Other Than Allergic Asthma

#### Nonatopic Asthma

A substantial proportion of patients with asthma has normal levels of total IgE and negative reactivity to tested aeroallergens.<sup>19</sup> In recent years, it has become increasingly evident that asthma is a heterogeneous disease, with numerous endotypes defined by different pathobiologic mechanisms.<sup>20</sup> In addition to T<sub>H</sub>2 bias, asthma may be sustained by diverse mechanisms, including T<sub>H</sub>17 polarization,<sup>21</sup> and immunogenic and immunomodulatory functions of the airway epithelium and group 2 innate lymphoid cells.<sup>22</sup> The pathogenesis of asthma in patients without atopy may involve environmental factors and be associated with neutrophils and innate immunity; however, some forms exhibit T<sub>H</sub>2-type airway inflammation with increased numbers of cells expressing FcεRI and increased expression of T<sub>H</sub>2 cytokines, suggesting that some patients with severe nonatopic asthma may benefit from anti-IgE therapy, even if an allergic trigger has not been identified. Pathway-specific biomarkers are needed to guide treatment choices.

**Table 1**  
Efficacy of omalizumab in patients with seasonal rhinitis

| Study                               | Design                          | Population                                 | Intervention                                                                                                    | Outcome measurements                                                                 | Findings                                                                                                                                    |
|-------------------------------------|---------------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Casale et al., <sup>61</sup> 1997   | 16-wk RPCT, dose ranging        | 240 patients                               | omalizumab 0.15 mg/kg IV or SC; or 0.5 mg/kg IV; or placebo                                                     | nasal symptom scores, antihistamine requirements                                     | dosages too low to suppress IgE levels                                                                                                      |
| Casale et al., <sup>30</sup> 2001   | 12-wk RPCT                      | 536 patients with IgE levels 151–700 IU/mL | omalizumab 50, 150, or 300 mg or placebo                                                                        | NSSS; antihistamine use; rhinitis-related QoL                                        | dose-dependent effects: decrease in IgE; decrease in NSSS vs placebo: 300 mg (0.84 vs 1.20, $P = .001$ ), 150 mg (0.95 vs 1.20, $P = .01$ ) |
| Adelroth et al., <sup>31</sup> 2000 | 8-wk RDBPCT                     | 251 patients                               | omalizumab 300 mg or (randomized 2:1) 4-wk intervals (3-wk intervals if total IgE $\geq 150$ IU/mL at baseline) | primary: NSSS; secondary: rescue antihistamine use, rhinoconjunctivitis-specific QoL | Significant differences in NSSS (LSM $-0.23$ , $P < .001$ ), antihistamine use and QoL                                                      |
| Okubo et al., <sup>32</sup> 2006    | 12-wk RDBPCT                    | 100 patients                               | omalizumab 150, 225, 300, or 375 mg or placebo                                                                  | composite end point: daily NSSS plus daily rescue medication use                     | composite end point: significantly lower for omalizumab LSM $\pm$ SE, $1.391 \pm 0.1769$ vs $2.499 \pm 0.1740$ ( $P < .001$ )               |
| Nagakura et al., <sup>62</sup> 2008 | 12-wk RDBCT with active control | 308 patients                               | omalizumab vs suplatast tosilate                                                                                | composite end point: daily NSSS plus daily rescue medication use                     | composite endpoint significantly lower for omalizumab ( $P < .001$ )                                                                        |

Abbreviations: IV, intravenously; LSM, least-squares mean; NSSS, nasal symptom severity score; QoL, quality of life; RDBCT, randomized, double-blinded, placebo-controlled trial; RPCT, randomized, placebo-controlled trial; SC, subcutaneously.

De Llano et al.<sup>23</sup> identified 29 patients with severe nonatopic asthma (Global Initiative for Asthma V) in the Spanish Severe Asthma Registry and compared them with 266 similarly treated patients with severe allergic asthma. Clinical improvement was not significantly different between groups after 2 years of follow-up. Recently, Garcia et al.<sup>24</sup> conducted a randomized, placebo-controlled, double-blinded study of omalizumab in 41 patients with severe nonatopic asthma. The primary end point in this proof-of-concept study was the change in Fc $\epsilon$ RI receptors on basophils and plasmacytoid DCs after 16 weeks; secondary end points included changes in lung function, asthma exacerbation rates, and assessments of asthma control. Lung function improved from baseline in the omalizumab group compared with placebo (forced expiration volume in 1 second +250 vs 0 mL,  $P = .032$ ); however, trends toward improvement in asthma scores and exacerbation rates were not statistically significant.

Results for 8 patients with nonatopic asthma and nasal polyps who were among patients treated with omalizumab in a 16-week randomized controlled clinical trial showed improvements in asthma symptoms and responses on the Asthma Quality of Life Questionnaire.<sup>25</sup> This suggests that at least some patients with severe nonatopic asthma may benefit from anti-IgE therapy, but larger trials are needed to identify endotypes associated with response to anti-IgE therapy.

Local production of allergen-specific IgE has been implicated in this condition. Local B-cell class switching and IgE production have been reported in patients without apparent atopy with negative systemic responses to allergen testing.<sup>26</sup> Locally produced IgE specific for staphylococcal enterotoxins has been associated with a 7-fold increase in the risk of asthma and an 11-fold increase in the risk of severe asthma.<sup>27</sup> Thus, regardless of the source of IgE, these patients may benefit from anti-IgE therapy to stabilize effector cells and decrease early and late responses. These findings support the concept of *localized allergy* in some patients that could identify a population of patients likely to respond to omalizumab therapy.

### Seasonal Allergic Rhinitis

Allergic rhinitis is an IgE-driven type I hypersensitivity with release of inflammatory mediators from mast cells and production of cytokines and chemokines associated with a T<sub>H</sub>2 response (Fig 1).<sup>28</sup> Analogously to nonatopic asthma, accumulating evidence has pointed to the role of local IgE production in some patients without apparent atopy.<sup>29</sup>

Some large controlled clinical trials have been conducted with omalizumab in *seasonal* allergic rhinitis (Table 1).<sup>30–32</sup> In a 12-week randomized, double-blinded, placebo-controlled dose-ranging trial by Casale et al.,<sup>30</sup> 536 patients were randomly assigned to receive 50, 150, or 300 mg of omalizumab or placebo just before the ragweed pollen season and then at intervals of 3 or 4 weeks depending on baseline total IgE levels. Nasal symptom severity scores were significantly lower in patients who received 300 mg of omalizumab compared with placebo and the decrease in IgE was associated with clinical benefit and decreased antihistamine use. Rhinitis-associated quality of life (QoL) was better in the group that received 300 mg of omalizumab compared with lower doses or placebo.

The efficacy of omalizumab for birch pollen-induced rhinitis was investigated in an 8-week randomized, double-blinded, placebo-controlled trial that enrolled 251 adults.<sup>31</sup> Omalizumab 300 mg ( $n = 165$ ) or placebo ( $n = 86$ ) was administered at 4-week intervals (3-week intervals if baseline total IgE was  $\geq 150$  IU/mL). Subjects receiving omalizumab had significant improvements in nasal symptom scores and QoL and used significantly less rescue medication.

**Table 2**  
Studies on treatment of nasal polyposis with omalizumab

| Study                               | Design                                                                        | Population                                    | Follow-up | Outcome measurements                                       | Findings                                                                                                                                        |
|-------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------|-----------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Penn and Mikula, <sup>41</sup> 2007 | retrospective case–control study                                              | 4 cases of atopic asthma                      | 10 mo     | endoscopic NP scores                                       | improvement in NP                                                                                                                               |
| Vennera et al, <sup>42</sup> 2011   | cohort study                                                                  | 10 patients with CRS                          | 16 mo     | sinus CT<br>nasal polyp size                               | scores vs presurgical values<br>significant decrease in polyp size                                                                              |
| Gevaert et al. <sup>25</sup> 2013   | randomized (2:1 omalizumab:placebo), double-blinded, placebo-controlled study | 24 patients (13 with atopy, 11 without atopy) | 16 wk     | INS usage<br>decrease in endoscopic NP score from baseline | significant decrease in INS use<br>scores significantly decreased with omalizumab (–2.67, $P = .001$ ) but not with placebo (–0.12, $P = .99$ ) |

Abbreviations: CRS, chronic rhinosinusitis; CT, computed tomography; INS, intranasal steroid; NP, nasal polyposis.

The efficacy of omalizumab for Japanese cedar seasonal allergic rhinitis was investigated in a randomized, placebo-controlled, double-blinded, 12-week trial that randomly assigned 100 subjects to receive placebo or 150, 225, 300, or 375 mg of omalizumab administered subcutaneously every 2 or 4 weeks depending on baseline IgE levels.<sup>32</sup> The composite primary end point was the sum of daily nasal symptom severity and daily nasal rescue medication scores. Omalizumab also was efficacious in this setting, with all end points showing significant improvement. A subset of subjects was retreated during pollen season the following year (open label) and efficacy and tolerability were similar. Thus, there is convincing evidence that anti-IgE therapy is effective in *seasonal* allergic rhinitis.

#### Perennial Allergic Rhinitis

Perennial allergic rhinitis can be difficult to treat, often requiring multiple therapies. Chervinsky et al<sup>33</sup> conducted a randomized, double-blinded, placebo-controlled trial in 289 subjects with confirmed sensitivity to dust or pet allergens. The study was timed to avoid the local pollen season. The primary outcome, mean nasal severity score, was significantly lower with omalizumab ( $P < .001$ ) and, as in studies conducted on patients with seasonal rhinitis, this result was supported by a significant decrease in antihistamine use ( $P < .005$ ) and improved rhinoconjunctivitis-specific QoL scores ( $P < .001$ ). This study confirmed the central role of IgE and established the efficacy of anti-IgE therapy in perennial allergic rhinitis.

#### Allergic Rhinitis and Asthma

Allergic rhinitis and allergic asthma share a common IgE-driven pathogenic mechanism and the 2 conditions often coexist. A cross-sectional study of 14,703 patients with asthma showed an allergic rhinitis prevalence of 55.2% (95% confidence interval 54.4–56.0).<sup>34</sup> Allergic rhinitis was strongly correlated with asthma severity and associated with poorer asthma control. Because of the similarities in immunopathology among allergic airway diseases and accumulating evidence that treating allergic rhinitis improves asthma control, guidelines suggest that therapy should address the 2 conditions.<sup>35</sup>

The efficacy of omalizumab for concomitant asthma and rhinitis was investigated in the SOLAR trial, a 28-week randomized, double-blinded, placebo-controlled study. Patients ( $n = 405$ ) had moderate to severe asthma with persistent allergic rhinitis and IgE levels from 30 to 1,300 IU/mL. Significantly fewer patients in the omalizumab group developed asthma exacerbations (20.6% vs 30.1%,  $P = .02$ ), and more patients reported clinically significant improvements on QoL measurements with omalizumab (57.7% vs 40.6%,  $P < .001$ ). Omalizumab also was more effective according to asthma and rhinitis symptom scores.<sup>36</sup> A post hoc analysis of the SOLAR trial showed that asthma response predicted rhinitis

response (odds ratio for asthma responders vs nonresponders 3.56, 95% confidence interval 1.94–6.54,  $P < .001$ ).<sup>37</sup>

Thus, there is robust evidence for benefit in allergic rhinitis; however, the cost of therapy may limit its role in this setting to severe or refractory disease, especially regarding perennial allergic rhinitis. The direct cost may be justified in patients with asthma that is complicated by seasonal rhinitis, if they are treated in conjunction with the pollen season.

#### Nasal Polyposis

Nasal polyposis is a common inflammatory condition associated with chronic rhinosinusitis that affects the nasal cavity and paranasal sinuses. Inflammation causes an accumulation of extracellular fluid and proliferation of mucosa and submucosa with formation of benign masses that can affect olfaction and cause congestion and painful nasal obstruction. Treatment involves intranasal or oral corticosteroids and endoscopic surgery, when indicated; however, the recurrence rate is high.

Originally considered an exclusively  $T_H2$  driven phenomenon, recently distinct NP endotypes have been described, with eosinophilic, neutrophilic, or mixed infiltrates and associated cytokine profiles.<sup>38</sup> Eosinophilic NP constitutes most cases in white patients, whereas the neutrophilic form is more common in Asian patients.<sup>39</sup> The eosinophilic endotype has been linked to high levels of local IgE production that is frequently specific for bacterial enterotoxins,<sup>40</sup> suggesting that IgE has a role in the pathogenesis of this endotype. Thus, anti-IgE therapy has been considered for these patients and several small studies have been conducted (Table 2).<sup>25,39,41,42</sup>

Penn and Mikula<sup>41</sup> reported a retrospective case–control analysis of 8 patients with atopic asthma who underwent endoscopic surgery for NP. Four patients received omalizumab postoperatively. There were no significant radiologic improvements after 10 months, but nasal polyp scores improved significantly in the group treated with omalizumab compared with presurgical values, suggesting that IgE may be involved in the re-formation of NP after removal; however, the small size and retrospective design limit the conclusions that can be drawn.

Guglielmo et al<sup>43</sup> reported a case of a 54-year-old man with asthma and NP that had relapsed twice after surgery. The recurrent NP was treated with topical and systemic corticosteroids. Serum total IgE level was 294 IU/mL. Frequent asthma exacerbations prompted the introduction of 225 mg of omalizumab every 2 weeks. Nasal symptoms were alleviated rapidly and corticosteroids were discontinued. Endoscopy showed normal mucosa with normalization of the hyperplastic sinus mucosa.

Vennera et al<sup>42</sup> described 19 patients with chronic rhinosinusitis and NP who were receiving omalizumab for severe asthma. Two thirds of patients had undergone at least 1 sinus surgery and the mean elapsed time since surgery was 29 months (range 18–39 months). Mean baseline serum total IgE was 257

IU/mL (range 115–328 IU/mL). Follow-up was 16 months (range 15–28 months), with endoscopic examinations at 3-month intervals. There were significant decreases in NP size and in intranasal corticosteroid use, and none of the patients needed additional surgery during the relatively long follow-up after surgery; however, there was no comparison group in this study.

Tajiri et al<sup>44</sup> prospectively evaluated the efficacy of omalizumab in 6 patients with NP and patients with severe allergic asthma and mean  $\pm$  SD total IgE levels of  $332 \pm 209$  IU/mL. After 16 weeks of therapy, the Lund-Mackay radiologic sinus score (primary end point) was significantly lower and this was correlated with changes in serum levels of periostin, a marker for eosinophilic airway inflammation. Rhinosinusitis-related QoL scores (Sino-Nasal Outcome Test 20) improved significantly, and nasal polyp size was decreased in 4 of 6 patients.

The effectiveness of anti-IgE therapy for NP was addressed in a randomized, double-blinded, placebo-controlled, 16-week trial of omalizumab conducted in 24 patients with nasal polyps and comorbid asthma.<sup>25</sup> Patients with ( $n = 13$ ) and without ( $n = 11$ ) atopy were included. Twenty-four patients were randomly assigned to receive omalizumab ( $n = 16$ ) or placebo. The primary end point was a decrease in total endoscopic nasal polyp scores; secondary end points included radiographic changes, nasal and asthma symptom scores, QoL, biomarker levels in serum, and nasal secretions.

Endoscopic nasal polyp scores after 16 weeks were significantly decreased from baseline with omalizumab ( $-2.67$ ,  $P = .001$ ) but not with placebo ( $-0.12$ ,  $P = .99$ ), and these results were confirmed by computed tomography. Omalizumab treatment was associated with significant improvements in nasal symptom scores, QoL scores, and responses on the Rhinosinusitis Outcome Measuring Instrument 31. These effects were similar in patients with and without atopy, suggesting that local IgE production may be driving NP. The effects of omalizumab on NP are consistent with a decrease in IgE and a subsequent decrease of Fc $\epsilon$ RI levels on effector cells in nasal mucosa and in polyp tissue.

The elevated levels of IgE in polyp tissue and nasal mucosa and the response to anti-IgE therapy support a role for IgE in the pathology of NP associated with asthma. However, the clinical significance of these effects is not known, and a similarly sized clinical trial conducted in patients with chronic rhinosinusitis showed no significant benefit compared with existing therapy.<sup>45</sup> Further controlled trials are needed, in which patients are stratified by endotype.

#### Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a strong T<sub>H</sub>2 response to *Aspergillus fumigatus* that results in recruitment of eosinophils, systemic eosinophilia, and elevated production of IgE that can lead to the development of bronchiectasis and progressive loss of lung function if not treated promptly. It occurs most often in patients with atopic asthma and in patients with cystic fibrosis (CF).<sup>46</sup> Systemic corticosteroids are effective but the condition often becomes steroid dependent. Elevated IgE and an intense T<sub>H</sub>2 reaction make ABPA a candidate for anti-IgE therapy, based on its ability to downregulate Fc $\epsilon$ RI on immune effector cells and APCs, decrease eosinophilia, and counter the strong T<sub>H</sub>2 bias. Accumulating evidence from case reports and series have pointed to the potential for omalizumab therapy to improve function and decrease corticosteroid use in these patients; however, controlled trials have not been reported.

There are several case reports and 3 case series involving a total of 38 patients without CF. Van der Ent et al<sup>47</sup> presented the case of a 51-year-old corticosteroid-dependent man with a total IgE level of 1,500 IU/mL and an eosinophil count of  $1,358/\text{mm}^3$  at presentation. He met all criteria for ABPA and was administered 375 mg of

omalizumab every 2 weeks. Asthma symptoms and biomarkers of eosinophilia showed improvement and oral corticosteroids were tapered but could not be stopped. Lung function did not improve. Zirbes and Milla<sup>48</sup> presented the case of a 33-year-old woman with a total IgE level of 3,090 IU/mL and eosinophilia at diagnosis. At 53 years of age, she started therapy with 375 mg of omalizumab every 2 weeks because of severe side effects from long-term corticosteroid use. Her corticosteroid dosage was decreased and there were no further exacerbations during 1 year of follow-up. Wong et al<sup>49</sup> reported on a retrospective case series with 4 corticosteroid-dependent adult patients treated with omalizumab for 12 months. Oral corticosteroid use was decreased in all patients, but none could discontinue. All patients showed improvements in asthma symptom scores and 3 of 4 had lower eosinophil counts; however, there was no consistent improvement in lung function.

Brinkmann et al<sup>50</sup> retrospectively identified a series of 18 patients with aspergillus-associated airway diseases who met Rosenberg's diagnostic criteria for ABPA. All patients had a positive skin test reaction for *Aspergillus* species and aspergillus-specific IgE; 17 of 18 had bronchiectasis and were receiving oral corticosteroids. The median IgE level was 698 IU/mL (interquartile range 478–977 IU/mL). Median follow-up while receiving omalizumab was 36 weeks (interquartile range 28–42 weeks). Median annual exacerbation rates were 1 (range 1–4) before and 0 (range 0–1) during therapy ( $P = .01$ ). The change in the number of patients receiving oral corticosteroids before and during therapy (17 of 18 and 6 of 18, respectively) was highly significant ( $P = .0005$ ). There was a marginally significant improvement in lung function. Five patients discontinued treatment owing to a lack of response.

These results are largely confirmed in a series of 16 cases of longstanding ABPA presented by Kanu and Patel.<sup>51</sup> All patients had received systemic corticosteroids in the previous year and 12 of 16 had bronchiectasis. Median serum IgE was 582 IU/L (range 131–3,766 IU/L). Comparisons between the year before initiating omalizumab treatment and the successive year showed significant decreases in exacerbations (median 4, range 0–12, vs 0, 0–4,  $P = .0001$ ) and oral steroid use (milligrams per day as prednisolone; median 8.5, range 0–60, vs 0, 0–10,  $P = .008$ ). Three of 9 patients receiving long-term systemic steroids were able to discontinue; 5 decreased consumption by at least 50%. However, no improvement was observed in lung function.

#### ABPA in Patients with CF

A steroid-sparing effect has been reported in several cases of steroid-dependent ABPA in patients with CF. Lebecque et al<sup>52</sup> reported on a steroid-dependent 12-year-old with pulmonary infiltrates, bronchiectasis, and a serum IgE level of 5,200 IU/mL. Administration of omalizumab resulted in improvement in lung function and allowed complete withdrawal of oral corticosteroid therapy. Elmallah et al<sup>53</sup> also observed a steroid-sparing effect in 3 steroid-dependent children with longstanding ABPA not responsive to antifungal therapy. Omalizumab 300 to 375 mg every 2 weeks improved lung function and decreased the frequency of exacerbations despite gradual withdrawal of oral corticosteroids. Homma et al<sup>54</sup> presented the long-term follow-up of 2 adolescents with steroid-dependent ABPA. The first patient had bronchiectasis. Administration of 300 mg of omalizumab every 4 weeks allowed tapering of oral corticosteroids over the course of 21 weeks, when clinical parameters improved. The second patient experienced an exacerbation when steroid dosage was tapered, but the steroids could be withdrawn completely after 16 months. Sastre et al<sup>55</sup> reported on the case of a 15-year-old patient with longstanding steroid-dependent ABPA that was unresponsive to antifungal therapy. Omalizumab 300 mg every 4 weeks improved lung function initially, but the patient developed a severe relapse and

remained dependent on a decreased dosage of corticosteroids after 12 months. Thus, 6 of these 7 patients with CF were able to discontinue oral corticosteroids; the patient who could not had a relatively low level of total IgE (248 IU/mL).

There are several reports of improvement in clinical parameters in patients with CF not receiving long-term treatment with oral corticosteroids. Collins et al.<sup>56</sup> treated a 13-year-old girl with a 5-year history of ABPA and intermittent oral corticosteroids for exacerbations. Omalizumab 300 mg every 2 weeks alleviated symptoms and improved lung function after the second dose. Pérez-de-Llano et al.<sup>57</sup> treated 2 children with recurring episodes of ABPA and high IgE levels at presentation (4,261 and 1,526 IU/mL). Omalizumab 375 mg every 2 weeks alleviated symptoms and normalized lung function after 2 to 3 weeks. Twenty weeks later, the 2 patients were stable. Tillie-Leblond et al.<sup>58</sup> reported on 2 patients 12 and 16 years old with longstanding ABPA characterized by bronchiectasis, elevated IgE (1,782 and 1,039 IU/mL), and decreased lung function (forced expiration volume in 1 second 39% and 36% of predicted). The 2 patients responded to omalizumab therapy with improvements in lung function and lower hospitalization rates. There is a strong evidence-based rationale for anti-IgE therapy in this condition owing to the involvement of IgE, and the observed responses are consistent with decreases in IgE and FcεRI that decrease the reactivity of mast cells and basophils and decrease eosinophilia. However, some patients who responded had extremely high pretreatment levels of total IgE that would not have been titrated by the omalizumab dosages administered. In patients with asthma, clinical response was found to correlate well with free total IgE levels and are optimal when levels are lowered to 50 ng/mL.<sup>59</sup> This phenomenon had been reported previously and may be explained by immunomodulatory effects that decrease IgE synthesis.<sup>17,18</sup> In fact, pharmacodynamic modeling based on clinical trial data predicts a decrease in IgE synthesis with omalizumab treatment.<sup>60</sup>

Thus, more than 50 cases have been published on the use of anti-IgE therapy in patients with ABPA. In many cases, response was associated with a steroid-sparing effect. Patients with CF had better responses in lung function and discontinuation of oral corticosteroids, perhaps owing to younger age and shorter disease duration. Controlled clinical trials are needed to confirm these observations and identify criteria for predicting response.

## Conclusions

Anti-IgE therapy with omalizumab is efficacious for severe allergic asthma not controlled by optimal conventional therapy and may decrease corticosteroid use in this population. Several other respiratory conditions have pathologic mechanisms that involve IgE. The evidence for clinical benefits is strongest in allergic rhinitis, in which large controlled trials have consolidated the evidence supporting efficacy; however, pharmacoeconomic considerations currently limit applicability. Patients with asthma who also have seasonal rhinitis may represent a population in which the benefit–cost ratio is more favorable, because therapy could coincide with and be limited to the local pollen season. Omalizumab therapy was marginally effective at improving lung function in a small controlled trial in patients with nonatopic asthma; however, it did not significantly improve asthma scores or exacerbation rates. Mechanisms driving the various endotypes are very heterogeneous and pathway-specific biomarkers are needed to determine whether anti-IgE therapy is more effective in specific endotypes. In patients with NP, omalizumab was shown to improve outcomes in a small controlled study; however, there are conflicting findings from a small controlled trial in chronic rhinosinusitis. Regarding ABPA, numerous case reports and several large case series have pointed to a potential benefit for patients with ABPA. Perhaps the most

relevant aspect to emerge is the consistent report of symptom control with lower corticosteroid dosages, with some patients able to discontinue them.

Thus, many IgE-driven respiratory conditions appear to respond to omalizumab treatment and warrant further investigation. Future controlled trials should include stratification by enterotype, where appropriate.

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