The efficacy of omalizumab treatment in patients with nonatopic severe asthma

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Abstract
Introduction: Nonatopic asthmatic patients generally have more severe clinical manifestations, frequently accompanied by chronic sinusitis and nasal polyps, with more limited therapeutic options as compared to atopic asthmatic patients. This has led to a search for novel therapeutic approaches, including omalizumab, for nonatopic asthmatic patients who are not adequately controlled with current therapies.

Materials and Methods: In this retrospective study undertaken between August 1, 2020, and December 31, 2021, at a tertiary allergy clinic, data from 61 patients with nonatopic asthma inadequately controlled with optimum therapy was examined.

Results: A total of 61 patients with severe asthma were included in the study [Female: 48 (78.7%), male: 13 (21.3%), mean age: 49 (18–71) years]. The mean duration of asthma was 60 (18–160) months. A statistically significant increase in Forced expiratory volume (FEV1 per second), forced vital capacity (FVC), and asthma control test (ACT) scores were found after 1 year of omalizumab treatment (p < 0.001, for all parameters). Omalizumab treatment was associated with a significant decrease in the number of asthma exacerbations, asthma-related hospitalizations, duration of hospitalizations, and several unplanned emergency room visits after 1 year (p < 0.001, for all parameters). A 1-year treatment with omalizumab led to significant changes in eosinophil counts and serum IgE levels (p < 0.001 and < 0.001, respectively).

Conclusion: In the severe atopic asthma patient group, omalizumab treatment provided similar clinical benefits to those observed in patients with severe atopic asthma, suggesting that it may be a useful therapeutic option in patients with nonatopic asthma who failed to benefit from treatments with steps 4 and 5.

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Introduction

Omalizumab is a humanized recombinant anti-immunoglobulin (Ig) E monoclonal antibody used to treat several allergic disorders.\(^1\) It binds to IgE heavy-chain, thereby reducing free IgE levels and preventing it from binding to its receptors on mast cells and basophils. Omalizumab has been approved for use in severe persistent allergic asthma and chronic urticaria resistant to antihistamines. In addition, based on the central role of IgE in the pathogenesis of many allergic disorders, “off-label” use of omalizumab has been a common practice, mainly for anaphylaxis, food allergies, and drug allergies, but also for other conditions such as allergic rhinitis, allergic bronchopulmonary aspergillosis, atopic dermatitis, nasal polyps, and Churg-Strauss syndrome.\(^2\)

The 2021 Global Initiative for Asthma (GINA) guidelines recommend omalizumab treatment for patients with moderate to severe asthma who are not controlled with step 4 or 5 treatments.\(^3\) Contrarily, the use of omalizumab in asthmatic patients is limited to atopic asthmatic patients, and the presence of atopy should be confirmed by demonstrating IgE-mediated sensitivity against at least one perennial allergen using skin prick or in vitro testing.\(^4\) However, both atopic and patients with nonatopic asthma exhibit a similar immunologic profile, including the elevation of cytokines such as IL-4 and IL-13, increased production of IgE, and increased expression of Fc-epsilon-RI (FceRI) mRNA. Furthermore, a multitude of studies have directly or indirectly shown that IgE plays a role in asthma pathogenesis independent of atopy.\(^5\) For instance, a five-fold increased occurrence of asthma has been detected in nonatopic patients with elevated total serum IgE levels.\(^6\) Patients with nonatopic asthma generally have more severe clinical manifestations frequently accompanied by chronic sinusitis and nasal polyps with more limited therapeutic options as compared to atopic asthmatic patients. This has led to a search for novel therapeutic approaches, including omalizumab, for nonatopic asthmatic patients who are not adequately controlled with current therapies. Studies of omalizumab in patients with nonatopic asthma are scarce in number and generally include case reports\(^7\)–\(^9\) or studies with relatively smaller sample sizes.\(^10\),\(^11\) Thus, in this retrospective study, we decided to examine the effect of omalizumab on clinical and laboratory parameters in a group of patients with nonatopic severe asthma who received at least one year of omalizumab treatment.

Materials and Methods

In this retrospective study undertaken between August 1, 2020, and December 31, 2021, at our Allergy and Immunology Unit of a Tertiary Center, data from 78 patients with nonatopic asthma inadequately controlled with optimum therapy was examined, following approval for “off-label” use of this agent from the Turkish Drug and Medical Device Agency of the Turkish Ministry of Health. Seventeen patients were excluded due to several reasons (e.g., short duration of omalizumab treatment precluding assessment of efficacy, treatment at another healthcare facility, or missing data in patient files), leaving 61 patients with nonatopic severe asthma for review.

Data on age, gender, smoking status, BMI (body mass index, kg/m\(^2\)), comorbid conditions (nasal polyps, chronic rhinosinusitis, and chronic urticaria), duration of asthma, and duration of omalizumab treatment were retrieved from patient files. Also recorded were pulmonary function test [FEV1 (Forced expiratory volume in one second), FVC (forced vital capacity), and FEV1/FVC] results and ACT (asthma control test) scores prior to the initiation of omalizumab treatment, oral corticosteroid dosage (daily) within the past year, and unplanned emergency room visits, number of asthma exacerbations, and hospitalizations in the past year. Pulmonary and clinical parameters were recorded again following 1 year of treatment with omalizumab.

Severe asthma was diagnosed based on GINA asthma guidelines.\(^12\) A nSpire ZAN 100 spirometer device was used for spirometry measurements.

Abbott Cell Dyn 3700 (Sheath reagent) and Siemens BN II/BN ProSpec system (particle-enhanced immunonephelometry) were used for automated complete blood counts and quantitative determination of serum immunoglobulin (Ig) E, respectively.

Patients underwent allergy testing using a skin-prick panel of 24 inhaled allergens from 8 classes (dog, cat, dust mite, grass, tree, ragweed, mold, and cockroach) (ALK, Abello, Madrid, Spain). A wheal diameter >5 mm with a flare at 20 min was considered a positive result, and patients were considered nonatopic in the absence of any reaction to any allergens or allergen-specific IgE.\(^13\)

Omalizumab (Xolair; Novartis, Basel, Switzerland) dosage was determined using the standard dosing scheme based on total serum IgE and bodyweight. Asthma was considered well controlled with an ACT score ≥20, partially controlled with an ACT score of 15–19, and poorly controlled with an ACT score <15.\(^14\)

The study protocol was approved by the Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine (meeting date: January 21, 2022, and decision no: 2022/3608).

All data obtained and recorded in the study forms were analyzed using IBM SPSS 20.0 (Chicago, IL, USA) statistical software program. The normal distribution of discrete and continuous numerical variables was tested with Kolmogorov-Smirnov test. Descriptive statistics for discrete and continuous numerical variables were expressed as mean ± standard deviation (SD) or median (minimum–maximum), whereas categorical variables were expressed as the number of cases and (%). Categorical variables were assessed using the chi-square test, while continuous variables were assessed using the t-test or the Mann-Whitney U test. Dependent variables with normal distribution were compared using the paired-samples t-test, whereas those without normal distribution were compared with the Wilcoxon test. Categorical-dependent variables with more than 2 nominal values were compared using the McNemar-Bowker test. A p value <0.05 was considered statistically significant.
Results

A total of 61 patients with severe asthma were included in the study [Female: 48 (78.7%), male: 13 (21.3%), mean age: 49 (18-71) years]. The mean duration of asthma was 60 (18-160) months. Main comorbidities included chronic rhinosinusitis (57.4%) and nasal polyps (24.6%). Clinical, laboratory and demographic parameters of the asthma patients are summarized in Table 1.

Compared with the baseline, a statistically significant increase in FEV1, FVC, and ACT scores was found after 1 year of omalizumab treatment (p < 0.001, for all parameters). After 1 year of omalizumab treatment, there was no significant change in FEV1/FVC (p = 0.095; Figure 1; Table 2). Furthermore, omalizumab treatment was associated with a significant decrease in the number of asthma exacerbations, asthma-related hospitalizations, duration of hospitalization, and unplanned emergency room visits after 1 year (p < 0.001, for all parameters; Table 2 and Figure 2).

Treatment for 1 year with omalizumab led to significant changes in the eosinophil counts and the serum IgE levels (p < 0.001 and 0.001, respectively) (Figure 3). Table 2 summarizes the changes in clinical and laboratory parameters after 1 year of omalizumab treatment.

Discussion

Literature data on the efficacy of omalizumab in patients with nonatopic asthma is scarce. In this study, evaluating the effect of omalizumab treatment in this patient group, we reached two important conclusions. First, omalizumab was associated with an increase in FEV1, FVC, and ACT scores, and a decrease in asthma exacerbations, asthma-related hospitalizations, length of hospital stay, and daily need for OCS among 61 patients with nonatopic severe asthma. Second, omalizumab treatment led to a decrease in eosinophil count and increased the serum total IgE level. These results suggest that omalizumab treatment may offer certain benefits in patients with nonatopic asthmatic who are unresponsive to other treatments.

Compared with atopic asthmatic patients, the nonatopic asthma patients have fewer therapeutic options, and until now, only a limited number of studies have assessed omalizumab use in nonatopic asthmatics. In a case report by Menzella et al., a 52-year-old patient with severe nonatopic asthma (receiving formoterol 18 mcg/day; budesonide 640 mcg/day; tiotropium bromide 18 mcg/day, and prednisone 25 mg/day) and a history of smoking, allergic rhinitis, and nasal polyps experienced significant symptomatic improvement with only 16 weeks of treatment with omalizumab. De Llano et al. observed an increased FEV1 and ACT scores and a reduced number of asthma exacerbations with omalizumab treatment in 29 nonatopic asthmatic patients, similar to those in atopic patients. In addition, Sözener et al. reported an increase in ACT scores and FEV1, and a decrease in asthma exacerbations, asthma-related hospitalizations, and daily oral corticosteroid dose among 13 patients with nonatopic asthma. Our results are similar and consistent with the previous observations.

IgE antibodies produced against common aeroallergens represent the main characteristic of atopic asthma. Bridging IgE molecules on mast cells and basophils by protein allergens results in the activation of these cells, leading to the release of preformed mediators such as histamine or newly formed mediators such as prostaglandins and leukotrienes from the mast cells. Therefore, both IgE and mast cells play important roles in the pathogenesis of asthma. Omalizumab prevents the interaction between IgE and its receptors by forming complexes with free IgE. Furthermore, it downregulates the Fc-epsilon-RI receptors found on the cell surface of basophils and mast cells. In Berger et al.’s study, incubation of bronchial tissue samples from asthmatic patients with omalizumab resulted in a decrease in specific and nonspecific bronchial hyperresponsiveness, which was postulated to be associated with the inhibition of bronchial mast cell degranulation.

Although these findings may suffice to explain the efficacy of omalizumab in patients with atopic asthma, other hypotheses have been put forward to account for the efficacy of omalizumab in nonatopic asthma patients. The first of these hypotheses involves a reduction in bronchial mucosal IgE positive mast cell numbers and anti-inflammatory effects, leading to clinical benefit. Another hypothesis

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Table 1 Clinical, demographic and laboratory parameters in asthma patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (18-71)</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>48 (78.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.42 ± 627</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>59 (96.8)</td>
</tr>
<tr>
<td>Ex-smoker (≥1 year)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td>60 (18-160)</td>
</tr>
<tr>
<td>Duration of omalizumab treatment, months</td>
<td>16 (12-66)</td>
</tr>
<tr>
<td>Dose of omalizumab</td>
<td></td>
</tr>
<tr>
<td>150 mg/4 weeks</td>
<td>22 (36.1)</td>
</tr>
<tr>
<td>300 mg/4 weeks</td>
<td>36 (59.0)</td>
</tr>
<tr>
<td>450 mg/4 weeks</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Main comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>35 (57.4)</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>15 (24.6)</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>HRCT findings of lungs</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23 (37.7)</td>
</tr>
<tr>
<td>Emphysematous changes</td>
<td>9 (14.8)</td>
</tr>
<tr>
<td>Bronchiectasis and ground-glass opacities</td>
<td>13 (21.3)</td>
</tr>
<tr>
<td>Linear atelectasis</td>
<td>10 (16.4)</td>
</tr>
<tr>
<td>Parenchymal fibrosis</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Mosaic perfusion</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

BMI: body mass index; HRCT: high-resolution computed tomography
points out to increased release of cytokines such as IL-4 and IL-13 via stimulation of intracellular pathways without cross-linking with allergens and direct binding of IgE to eosinophils, neutrophils, and monocytes, activating these cells. Omalizumab treatment was shown to result in reduced sputum eosinophil counts and a decrease in CD4+ and CD8+ lymphocytes, B lymphocytes, and interleukin-4 positive cells; however, a similar mechanism of action is yet to be confirmed in nonatopic asthma patients. Based on this hypothesis, omalizumab is expected to reduce eosinophil counts by decreasing IL-4 and IL-13 secretion, also in patients with nonatopic asthma. The significant reduction in eosinophil counts after 1 year of omalizumab treatment in our study may be related with this mechanism. Another
hypothesis is based on the observation that nonatopic asthmatic patients have more frequent symptoms and more extensive airway obstruction, suggesting that all asthma patients have an atopic component and increased IgE may result from a yet-undefined allergen. The latter hypothesis should be tested in larger patient samples to better elucidate the efficacy of omalizumab in patients with nonatopic asthma.

Our study has certain advantages and limitations. The advantages include a relatively larger sample size and data based on real-life observations. In contrast, the cross-sectional design represents its major disadvantage. In addition, although patients were considered atopic based on skin prick testing and in vitro testing, some patients might have been sensitized through allergens not tested with our study panels. However, since atopy is reduced with age,
and our patients mostly comprised middle- to advanced-age individuals, it may be assumed that some patients with previous allergen sensitivity may have experienced reduced sensitivity over time, leading to their classification in the nonatopic category with subsequent false negativity. Additionally, since our study only assessed a 1-year period of omalizumab treatment, our results may not be generalized to longer-term efficacy.

In conclusion, in this patient group, omalizumab treatment provided similar clinical benefits to those observed in patients with severe atopic asthma, suggesting that it may be a useful therapeutic option in patients with nonatopic asthma who failed to benefit from step 4 and step 5 treatments.

References


