Effects of Adding Omalizumab, an Anti-Immunoglobulin E Antibody, on Airway Wall Thickening in Asthma

Makoto Hoshino a Junichi Ohtawa b

Departments of Respiratory Medicine and Radiology, Atami Hospital, International University of Health and Welfare, Atami, Japan

Abstract

Background: Omalizumab may inhibit allergic inflammation and could contribute to decreasing airway remodeling in patients with asthma. Objective: The aim of this study was to assess the effects of omalizumab on airway wall thickness using computed tomography (CT). Methods: Thirty patients with severe persistent asthma were randomized to conventional therapy with (n = 14) or without omalizumab (n = 16) for 16 weeks. The following airway dimensions were assessed by a validated CT technique: airway wall area corrected for body surface area (WA/BSA), percentage wall area (WA%), wall thickness (T)/BSA, and luminal area (Ai)/BSA at the right apical segmental bronchus. The percentage of eosinophils in induced sputum, pulmonary function and the Asthma Quality of Life Questionnaire (AQLQ) were assessed as well. Results: Treatment with omalizumab significantly decreased WA/BSA (p < 0.01), WA% (p < 0.01), and T/BSA (p < 0.01), and increased Ai/BSA (p < 0.05), whereas conventional therapy resulted in no change. In the omalizumab group (n = 14), a significant decrease in the percentage of sputum eosinophils (p < 0.01), improved forced expiratory volume in 1 s (FEV1), and an improved AQLQ score were recorded. The changes in FEV1% predicted and sputum eosinophils were significantly correlated with changes in WA% (r = 0.88, p < 0.001, and r = 0.72, p < 0.01, respectively). Conclusions: These findings suggest that omalizumab reduced airway wall thickness and airway inflammation. Larger patient studies with longer-term follow-up are needed to show whether omalizumab can truly maintain improved airway wall dimensions.

Introduction

Allergic asthma is defined by the presence of immunoglobulin E (IgE) antibodies against one or more common environmental allergens, such as house dust mite, animal dander, pollens and moulds [1]. The risk of developing asthma increases with increasing IgE levels [2]. Omalizumab, a humanized recombinant murine monoclonal anti-IgE antibody, was designed to treat patients with allergic asthma by reducing the circulating pool of IgE able to bind to high-affinity IgE receptor [3, 4]. In this

Key Words

Airway inflammation · Airway wall thickness · Anti-immunoglobulin E antibody · Asthma · Computed tomography
In a 28-week, randomized, placebo-controlled trial in the European Union (INNOVATE study), omalizumab significantly reduced oral corticosteroid use, exacerbations and total emergency visit rates, and significantly improved lung function, asthma symptoms and quality of life [12].

Asthma is characterized by episodic airflow obstruction or limitation, which involves several inflammatory cells and the interaction of many different mediators. Airway remodeling is triggered by long-term, uncontrolled airway inflammation [13]. Over time, the airways undergo structural changes, such as thickening of airway wall and increased mucus production, which can become permanent if not adequately treated and severely impair lung function [14]. Although histological findings show a significant increase in subepithelial basement membrane thickening, bronchial biopsy is difficult to obtain and/or is invasive. Airway wall thickening has also been evaluated noninvasively in asthma using high-resolution computed tomography [15–18]. Indeed, the degree of wall thickness has been correlated with disease severity [15, 17] and airflow limitation [17, 18].

The anti-inflammatory activity of omalizumab was established not only in peripheral blood eosinophils [19] but also in a biopsy study in asthma patients [20]. However, there is limited knowledge about the effects of omalizumab on airway dimensions. The aim of the present study was to assess the effects of omalizumab on wall thickness using CT in patients with severe persistent asthma and to establish a possible correlation of these measurements with other parameters of airway inflammation.

**Subjects and Methods**

**Subjects**

Male and female, nonsmokers aged 20–75 years, with severe allergic asthma, who were symptomatic despite treatment with a high-dose inhaled corticosteroid (ICS) plus a long-acting inhaled \( \beta_2 \)-agonist (LABA), were eligible if they met the following criteria: positive immediate responses on skin prick test to at least one common perennial allergen (Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat dander or dog dander); total serum IgE \( \geq 30 \) to \( \leq 700 \) IU/ml; forced expiratory volume in 1 s (FEV\(_1\)) reversibility of \( > 12\% \) after inhalation of 200 \( \mu \)g salbutamol; methacholine provocation concentration causing a 20% fall in FEV\(_1\) < 8 mg/ml; treatment with \( \geq 400 \) \( \mu \)g fluticasone propionate or its equivalent ICS and LABA for 8 weeks; other asthma medications, including theophylline and anti-leukotrienes taken regularly from \( \geq 8 \) weeks prior to randomization, were permitted; maintenance oral corticosteroids (maximum prednisolone 20 mg/day) were permitted providing at least one exacerbation had occurred in the previous year. Severe asthma was considered not to be well controlled if patients had persistent asthma symptoms with an ICS plus a LABA, defined as an average of 1 or more nighttime awakenings per week and daytime asthma symptoms requiring the use of rescue medication for 2 or more days per week [1, 21]. The exclusion criteria were the following: prior omalizumab treatment; requirement of omalizumab doses of \( > 750 \) mg per 4 weeks on the basis of serum IgE and body weight; treatment for an exacerbation within 4 weeks of randomization. Each subject provided written, informed consent before enrollment. The study was approved by the Institutional Review Board at our hospital and was registered at http://www.umin.ac.jp, with the identifier: No. UMIN 000002765.

**Study Design**

This was a randomized, controlled, open-label study with a 16-week treatment phase to assess airway dimensions, sputum eosinophils, pulmonary function, and QoL. The study comprised an 8-week run-in phase and a 16-week treatment with conventional therapy as recommended by Global Initiative for Asthma (GINA) with or without omalizumab [1]. During the first 4 weeks of the run-in period, the dose of ICS was adjusted upward or downward to maintain previous asthma control. The patients were monitored to ensure both the presence of asthma symptoms at levels acceptable to the patients and investigators. The doses of ICS, LABA, and other concomitant asthma medications were kept constant in the last 4 weeks of the run-in period prior to randomization and were maintained during the treatment period. During the treatment phase, patients made study visits at weeks 0, 4, 8, 12, and 16 (additional visits if injections every 2 weeks were required). Patients were permitted short-acting \( \beta_2 \)-agonist rescue use as required. The dose of omalizumab was at least 0.016 mg/kg/IgE (IU/ml) every 2 or 4 weeks. Patients were treated subcutaneously with omalizumab (150–300 mg every 4 weeks or 225–375 mg every 2 weeks) on the basis of the serum total IgE concentration and patient body weight at baseline [22].

**Airway Measurement**

Quantitative image analysis of CT scans (Toshiba Medical, Tokyo, Japan) was performed at full inspiration using the following parameters: 120 kV, 200 mA, 0.5 s rotation time, pitch 0.83, and 0.5 mm collimation. Data were reconstructed with high spatial resolution, with a 1-mm reconstruction section thickness, 0.5 mm interval, and a 512 \( \times \) 512 matrix. Images were displayed on a window width of 1,600 HU and a window level of –600 HU. The dimensions of the right upper lobe apical segmental bronchus (RBL) were analyzed by the following procedure. A semi-automated program using the full-width half-maximum technique was used to determine the accuracy and repeatability of a non-biased objective measure of edge detection in airway wall cross-sectional images [23]. The following airway parameters were then computed automatically by the program: luminal area (Ai), outer area of the airway (Ao), wall area (WA = Ao – Ai), percentage wall area (WA\% = WA/Ao \( \times \) 100), and absolute wall thickness (T). Assuming the hypothesis that bronchi are round on cross-sectional reformatted sections, absolute T was calculated as the difference between the total bronchus radius and the lumen radius: \( (\sqrt{Ao/\pi}) – \sqrt{(Ai/\pi)} \). Because airway size may be affected by body...
Airway wall thickness was estimated as \( \frac{\text{WA}}{\text{BSA}} \), \( \text{WA\%} \), and \( \frac{T}{\text{H2O}} \). To assess changes in lung volume, the cross-sectional area of the lung was measured before and after treatment by tracing the outer perimeter of the lung parenchyma on the same slice as that used for measurement of airway dimensions [24]. After the name of the patient and the date of the examination were deleted, the images were analyzed in random order by a radiologist (J.O.).

**Sputum Induction**

Sputum induction and processing were performed according to the methods of Fahy et al. [25] with a slight modification [26]. Briefly, subjects inhaled a 5% hypertonic saline solution from an ultrasonic nebulizer for 15 min, and adequate plugs of sputum were separated from saliva. After treatment with 0.1% dithiothreitol (Sputasol, Oxoid Ltd., Basingstoke, UK), the sample was cytocentrifuged and cells were stained by the May-Grünwald-Giemsa method. Differential cell counts were expressed as a percentage of 400 nonsquamous cells.

**Pulmonary Function**

All subjects underwent standard spirometric measures of lung function according to the American Thoracic Society guidelines [27]. FEV\(_1\), forced vital capacity, and morning peak expiratory flow (PEF) were measured.

**Quality of Life**

The Asthma Quality of Life Questionnaire (AQLQ) contained 32 items covering five domains (symptoms, activities, emotions, environmental and overall) using a 7-point scale [28]. A change of >0.5 point represents a clinically meaningful improvement in AQLQ.

---

**Table 1. Patients’ baseline demographic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>With omalizumab (n = 14)</th>
<th>Without omalizumab (n = 16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, M/F</strong></td>
<td>3/11</td>
<td>4/12</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>59.2 (11.4)</td>
<td>51.2 (18.7)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>BSA, m(^2)</strong></td>
<td>1.56 (0.17)</td>
<td>1.59 (0.25)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Disease duration, years</strong></td>
<td>16.3 (11.5)</td>
<td>10.9 (7.2)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Serum total IgE, IU/ml</strong></td>
<td>248.0 (170.3)</td>
<td>282.0 (192.5)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Morning PEF, liters/min</strong></td>
<td>223.6 (116.9)</td>
<td>239.6 (57.3)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>FEV(_1), % predicted</strong></td>
<td>65.3 (13.9)</td>
<td>68.4 (12.2)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>FEV(_1), liters</strong></td>
<td>1.32 (0.6)</td>
<td>1.43 (0.41)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>PC(_{20}), mg/ml</strong></td>
<td>1.64 (1.76)</td>
<td>1.94 (1.66)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Medication**

- **ICS, µg/day\(^1\)**: 791.4 (246.4) vs. 862.5 (305.2), p = 0.24
- **LABA, n**: 14 vs. 16
- **Antileukotriene, n**: 10 vs. 12
- **Theophylline, n**: 6 vs. 7
- **Oral corticosteroid, n**: 4 vs. 5

Data are presented as means and SDs (shown in parentheses). PC\(_{20}\) = Provocation concentration of methacholine causing a 20% fall in FEV\(_1\).

\(^1\) Fluticasone propionate equivalent.

---

**Analysis**

As no data evaluating the effects of omalizumab on airways using CT were available in the literature, no hypothesis was formulated for this exploratory study. It was scheduled to include a total of 30 subjects in the study in order to obtain 14 patients with omalizumab and 16 patients without omalizumab (conventional therapy) with evaluable CT sets of data in the whole treatment period. Values were presented as means ± SD and median and range (in parentheses). Comparisons for quantitative variables were performed by nonparametric analysis, Mann-Whitney and Kruskall-Wallis tests for nonrelated samples. Comparisons at two different times were carried out using Wilcoxon’s test for related samples. The correlation between airway wall thickness and pulmonary function, sputum eosinophils was analyzed using the Spearman rank correlation coefficient. A p value <0.05 was considered significant. All data were analyzed using StatView software (SAS Institute, Cary, N.C., USA).

**Results**

Thirty subjects completed the full protocol (with omalizumab, n = 14; without omalizumab, n = 16), of those 22 had matched sputum samples (with omalizumab, n = 12; without omalizumab, n = 10). The characteristics of the subjects are shown in Table 1. There were no significant differences between the groups in any of the studied parameters.
CT Measurements

No differences in bronchial morphometric parameters were found between the groups at baseline when the analysis was performed. In the omalizumab-treated group, WA/BSA, WA%, and T/H20906/BSA were significantly reduced at the end of the study compared to the initial values [13.7 mm²/m² (7.4–17.3) to 12.1 mm²/m² (4.8–15.6), 71.1% (58.9–79.6) to 64.7% (41.2–75.9), 1.21 mm/m (0.84–1.43) to 0.92 mm/m (0.79–1.11), respectively; all p < 0.01]. No significant changes in WA/BSA, WA%, and T/H20906/BSA were observed in the subjects with conventional therapy [11.9 mm²/m² (8.3–15.3) to 13.1 mm²/m² (5.9–16.3), 67.2% (57.8–78.0) to 69.2% (59.0–77.6), 1.12 mm/m (0.76–1.32) to 1.11 mm/m (0.69–1.37)]. Furthermore, omalizumab significantly increased Ai/BSA [4.8 mm²/m² (2.4–7.8) to 6.4 mm²/m² (2.9–8.4), p < 0.05], but there were no significant changes in the group on conventional therapy without omalizumab [5.3 mm²/m² (2.3–8.6) to 5.4 mm²/m² (2.4–8.5)] (fig. 1). Lung area did not change versus before treatment in either group (data not shown).

Induced Sputum

The median (range) percentage of eosinophils in induced sputum significantly decreased from 6.0% (1.2–14.1) to 2.0% (0–3.7) in the subjects treated with omalizumab (p < 0.001), but did not change [from 5.3% (1.5–12.6) to 4.8% (0–11.0)] in those treated without omalizumab (fig. 2).

Pulmonary Function

Treatment with omalizumab resulted in significant increases versus before in FEV₁ (1.32 ± 0.60 to 1.53 ± 0.56 liters, p < 0.05), FEV₁% predicted (65.3 ± 13.9 to 73.5 ± 11.9%, p < 0.01), morning PEF (223.6 ± 111.6 to 260.3 ± 109.3 liters/min, p < 0.01) to the end of the study. However, no significant differences were observed in these pulmonary function indices in the subjects undergoing conventional treatment without omalizumab (table 2). The changes in WA% after treatment with omalizumab were correlated with the change in FEV₁% predicted (r = 0.88, p < 0.001) and the change in sputum eosinophils (r = 0.72, p < 0.01) (fig. 3).

Asthma Quality of Life Questionnaire

Domain analysis revealed that significantly better scores in each domain contributed to the overall improvement of total AQLQ in the omalizumab group (differences in symptoms 1.35, activities 1.56, emotions 1.52, environmental 1.46, and overall 1.47). However, in the group treated with conventional therapy without omalizumab
zumab, AQLQ scores were not significantly different compared to baseline (differences in symptoms 0.38, activities 0.12, emotions 0.23, environmental 0.37, and overall 0.28) (fig. 4).

Discussion

This study showed that 16 weeks of treatment with omalizumab reduced airway wall thickness. The change in wall thickness was associated with a marked reduction in sputum eosinophils, and improvement in pulmonary function and quality of life. To the best of our knowledge, this is the first clinical study to demonstrate improvement in airway dimensions after treatment with anti-IgE in asthma patients.

Airway remodeling, i.e. airway structural alterations, such as goblet cell hyperplasia, subepithelial fibrosis, increased smooth muscle mass, and angiogenesis, plays an important role in the pathophysiology of asthma. Remodeling is assumed to result in persistent airflow limitation, decreased lung function, and airway hyperresponsiveness. Some studies have reported that ICS may reduce basement membrane thickness in asthmatic subjects and may therefore influence subepithelial fibrosis, a major feature of remodeling [29–32]. On the other hand, other studies have reported a modest or no effect on basement membrane thickness [33, 34]. These conflicting data could be related to the dose and duration of ICS therapy. Nevertheless, bronchial biopsy is not easy to perform in clinical practice due to its invasive nature. CT imaging of the airways has been developed as a technique to study asthmatic airway remodeling in vivo [17, 18], and attempts have been made to correlate CT findings of airway remodeling to measures of lung function [35]. In the current study, omalizumab was effective in reducing wall thickness and eosinophilic airway inflammation. The mechanism of airway wall thickening that responds to treatment may include inflammatory processes since previous studies reported that treatment with omalizumab significantly reduced the number of inflammatory cells [19, 20, 36]. However, our study included only a small number of patients. Studies on larger numbers of patients together with a long-term follow-up are needed to see
whether omalizumab can truly alter airway wall thickness and whether changing airway wall thickness actually does produce a functional benefit.

Multidetector row CT demonstrated that a salmeterol/fluticasone combination did not significantly change either WA or Ai in patients with poor asthma control [37]. We may find that omalizumab, as an add-on to current asthma therapy, offers a potential explanation for decreasing airway wall thickness. Some cytokines and growth factors (e.g. transforming growth factor-β1) associated with airway inflammation play important roles in airway remodeling and may be responsible for the increased eosinophils and wall thickness in asthmatic airways [38, 39]. Furthermore, vascular endothelial factor plays an important role in angiogenesis, and colocalization studies show that macrophages, eosinophils and CD34+ cells are major sources of vascular endothelial factor [40]. Downregulation of endothelin-1 in exhaled breath condensate after omalizumab therapy significantly correlated with a decrease in markers of allergic inflammation such as exhaled nitric oxide and serum eosinophil cationic protein [41]. Eosinophil apoptosis and reduced numbers of lymphocytes producing granulocyte macrophage colony-stimulating factor have been observed in omalizumab-treated patients with asthma, which may also contribute to the inhibitory action of omalizumab on eosinophils [19]. Recently, omalizumab decreased the concentration of RANTES in exhaled breath condensate and exhaled nitric oxide in severe allergic asthma [42]. RANTES is recognized as a potent eosinophil chemotactic and activation factor that induces the secretion of bronchoconstrictive mediators [43]. The decrease in wall thickness significantly correlated with the downregulation of sputum eosinophils. Components
of wall thickness, such as airway mucosal edema, mucus cell hyperplasia, and increased vascularity may be modified by omalizumab. Niimi et al. [44] showed that in a population including a majority of patients with moderate or severe asthma, airway wall thickening as assessed by CT partially responded to treatment with ICS, and these effects reflect reduced airway inflammation. This inhibitory effect of omalizumab on eosinophils may be explained at a molecular level. The change in luminal area after treatment with omalizumab could reflect potential effects of lung volume on airway dimensions [24]. However, such effects were unlikely because lung area was not significantly different versus baseline values.

It has been reported that treatment with omalizumab increases FEV₁ and PEF when compared with placebo [8, 12, 45], and the current study now demonstrated a similar action with respect to pulmonary function.

The efficacy of omalizumab in the improvement of asthma symptoms has been described in numerous studies in the last decade. A significant improvement in AQLQ occurred in patients after treatment with omalizumab, and these results confirm findings from previous studies in asthma [8–10, 12, 45, 46]. The cost of omalizumab is USD 260, and depending on dosages, the cost/year may vary between USD 3,200 and 19,000. A recent study by Wu et al. [47] assessed the cost effectiveness of omalizumab in the treatment of asthmatic patients.

There are some limitations to the current study. First, the current study included only a small number of patients in each arm. Reducing airway wall thickness is usually assimilated to reducing airway remodeling, and controlling airway remodeling is a critical issue that has not been solved by current asthma treatments. However, it is still controversial whether even inhaled corticosteroids are the best treatment for asthma patients capable of inhibiting airway remodeling. Due to the small numbers of participants in this study (n = 14) a lot of inferences – that may be statistically biased – are being made from this treatment. Second, this was an open-label study that did not include a placebo group as placebo treatment could have raised ethical issues. The potential for bias to be introduced by patients and investigators in the assessment of outcomes should be considered when interpreting open-label data. Third, only the RBI was assessed. However, a recent study suggested that airflow measurements of RBI correlated with other proximal airways, which averaged more than 19 segmental bronchi [48]. Placebo-controlled, long-term, and large-scale studies are needed to determine whether omalizumab can modify the progressive nature of asthma. In spite of these limitations, the present findings provide an important addition to the available evidence on potential treatment options of severe asthma.

In conclusion, omalizumab, as an add-on to current asthma therapy, significantly improved disease control in terms of improving pulmonary function, with a reduction in airway wall thickness and eosinophilic inflammation.

Acknowledgements

The authors would like to thank the staff of the Division of Internal Medicine and the Department of Laboratory Medicine, Atami Hospital International University of Health and Welfare.

Financial Disclosure and Conflicts of Interest

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of the manuscript.

References


Effects of Omalizumab on Airway Wall Thickening


