Ann Allergy Asthma Immunol 113 (2014) 470–475

Contents lists available at ScienceDirect

Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study

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ARTICLE INFO

Article history:
Received for publication January 13, 2014.
Received in revised form June 2, 2014.
Accepted for publication June 5, 2014.

ABSTRACT

Background: Omalizumab, a humanized anti-IgE monoclonal antibody, is reportedly an effective treatment for severe allergic asthma. However, there have been few comprehensive analyses of its efficacy, including assessments of small airways or airway remodeling.
Objective: To comprehensively evaluate the efficacy of omalizumab, including its effects on small airways and airway remodeling, in adult patients with severe refractory asthma.
Methods: In this prospective, time-series, single-arm observational study, 31 adult patients with severe refractory asthma despite the use of multiple controller medications, including high-dose inhaled corticosteroids (1,432 ± 581 μg/d of fluticasone propionate equivalent), were enrolled. Clinical variables, including Asthma Quality of Life Questionnaire, asthma exacerbations, exhaled nitric oxide, pulmonary function, methacholine airway responsiveness, induced sputum, and chest computed tomogram, were assessed at baseline and after 16 and 48 weeks of treatment with omalizumab.
Results: Twenty-six of the 31 patients completed 48 weeks of treatment. For these patients, Asthma Quality of Life Questionnaire scores and peak expiratory flow values significantly and continuously improved throughout the 48 weeks ($P < .001$ for all comparisons). Unscheduled physician visits, asthma exacerbations requiring systemic corticosteroids, fractional exhaled nitric oxide at 50 mL/s and alveolar nitric oxide levels, sputum eosinophil proportions, and airway-wall thickness as assessed by computed tomography significantly decreased at 48 weeks ($P < .05$ for all comparisons).
Conclusion: Omalizumab was effective for adult patients with severe refractory asthma. Omalizumab may have anti-inflammatory effects on small airways and reverse airway remodeling.
Trial registration: UMIN000002389.

Introduction

Immunoglobulin E (IgE) plays a central role in the pathophysiology of allergic asthma. Serum IgE levels are positively correlated with airway hyperresponsiveness,[1] asthma symptoms, and asthma severity.[2] Omalizumab is a humanized anti-IgE monoclonal antibody that binds to serum free IgE. By decreasing serum free IgE levels and the expression of high-affinity IgE receptors on mast cells and basophils, omalizumab has various clinical effects on moderate-to-severe asthma,[3–6] such as decreasing asthma exacerbations and airway inflammation and improving asthma-related quality of life and pulmonary function reflecting mainly large airways. However, its possible anti-inflammatory or physiologic effects on small airways have not been clarified.

Airway remodeling is a cardinal feature of asthma and is characterized by thickening of the lamina reticularis and structural changes to the epithelium, submucosa, smooth muscle, and vasculature of the airway wall.[7] Airway remodeling is associated with pathophysiologic features, particularly disease severity.[7,8] Although its pathogenesis is not fully understood, persistent inflammation may be responsible. Conventional therapies, including inhaled corticosteroid (ICS), do not consistently reverse remodeled airways.[7]

In the authors' previous studies, 12-week treatment with ICS decreased airway-wall thickness as assessed by computed tomography (CT) in steroid-naive asthmatics,[9] which was associated with

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Disclosure: Dr Matsumoto received remuneration from lectures sponsored by Novartis. The other authors have nothing to disclose.

http://dx.doi.org/10.1016/j.anai.2014.06.004
1081-1206/

a decrease in airway inflammation. However, further long-term treatment (mean 4.2 years) with ICS did not affect airway-wall thickness.[10] Omalizumab would be expected to reverse the remodeled airways because of its effects on allergic asthma pathophysiology.[11] However, there are only a limited number of reports on the effects of omalizumab on airway remodeling.[12,13]

In this study, the authors comprehensively evaluated the efficacy of omalizumab, including its effects on small airways and airway remodeling, in adult patients with severe refractory asthma.

Methods

Study Design and Patients

This was a prospective, single-arm, observational study. The study protocol (UMIN000002389) was approved by the ethics committee of Kyoto University (Kyoto, Japan), and written informed consent was obtained from all participants.

Adult patients with severe refractory asthma were enrolled at the asthma clinic of Kyoto University Hospital from July 2009 to August 2011. Asthma was diagnosed based on the Global Initiative for Asthma guidelines of 2006.[14] Asthma was poorly controlled in all patients, even with the concomitant use of long-acting β_2 agonists, leukotriene receptor antagonists, or theophylline, in addition to high-dose ICSs or concomitant oral corticosteroids. Additional inclusion criteria were total serum IgE levels up to 700 IU/mL and body weight of 30 to 150 kg. All patients had at least 1 positive result for serum-specific IgE or 1 positive intradermal test result for common aeroallergens. Exclusion criteria were (1) a history of anaphylactic reactions to omalizumab, (2) active lung diseases other than asthma, (3) pregnant or nursing women, (4) elevated IgE from diseases other than atopy, and (5) a smoking history of more than 10 pack-years or within the previous 1 year.

Study Protocol

Omalizumab was administered subcutaneously every 2 to 4 weeks, with dosing based on body weight and baseline total serum IgE levels. The following clinical variables were assessed at baseline and at 16 and 48 weeks of treatment: asthma-related health status as assessed using the St George's Respiratory Questionnaire (SGRQ)[15] and Asthma Quality of Life Questionnaire (AQLQ)[16]; asthma control as assessed using the Asthma Control Questionnaire (ACQ)[17]; rates of unscheduled physician visits; asthma exacerbations that required systemic corticosteroids for at least 3 days; hospitalization; peak expiratory flow (PEF); exhaled nitric oxide (eNO) levels; pre-bronchodilator pulmonary function, including impulse oscillometry (IOS); methacholine airway responsiveness; induced sputum; and CT measurements. These variables, except CT measurements, are routinely assessed in the authors' asthma clinic. All variables and cost of treatment were covered by the Health-Insurance-For-All health insurance system of Japan.

During omalizumab treatment, baseline ICS doses were not altered unless patients strongly requested a decrease (n = 3).

Peak Expiratory Flow

Morning and evening PEF values were determined using a Personal Best Peak Flow Meter (HealthScan Products Inc, Chicago, Illinois); the best of 3 measurements was recorded in a diary. Mean PEF values during 4 weeks before baseline and after 16 and 48 weeks of treatment were analyzed.

eNO Analysis

Exhaled NO levels were determined with a chemiluminescence analyzer (NOA 280; Sievers, Boulder, Colorado). Fractional eNO (FeNO) levels were determined at 3 expiratory flows of 50 (FeNO50), 100, and 200 mL/s. Alveolar NO (CA_{NO}) was calculated using the equation CA_{NO} = slope − intercept/740, after plotting NO output (ie, eNO level × expiratory flow).[18]

Pulmonary Function

After eNO measurements, respiratory impedance was measured using a Jaeger Master Screen IOS (Erich Jaeger, Hoechberg, Germany) according to standard recommendations. The authors measured respiratory resistance (Rrs) at 5 Hz (R5) and 20 Hz (R20), the difference between R5 and R20 and the integrated area of low-frequency reactance, as proxies of total and large airway resistance, and ventilation heterogeneity or small airway disease.[19,20]

After IOS measurements, vital capacity (VC), forced VC, forced expiratory volume in 1 second (FEV_1), forced expiratory flow at 25% to 75% (FEF_{25-75}), ratio of residual volume to total lung capacity, and the slope of phase 3 of the nitrogen single-breath washout curve were determined using a Chestac-8800 (Chest, Tokyo, Japan).

Methacholine Challenge

Airway responsiveness was assessed by measuring Rrs (centimeters of H_2O per liter per second; Astograph; Chest, Tokyo, Japan) under continuous methacholine inhalation.[21] The index of airway sensitivity was Dmin (ie, the cumulative dose of methacholine at the inflection point where Rrs began to continuously increase). The slope of the methacholine and Rrs dose–response curve was used as an index of airway reactivity.[21]

Sputum Induction and Processing

Sputum was induced and processed as described previously.[22] Cell differentials were determined by counting at least 400 non-squamous cells after staining with May-Grünwald-Giemsa stain.

Allergen Tests

Serum total IgE levels and levels of specific IgE antibodies against 9 common aeroallergens were determined using radioimmunosorbent tests (Pharmacia, Upjohn, Tokyo, Japan). For cases in which all serum specific IgE antibody results were negative, intradermal tests were performed for 15 allergens.

CT Analysis of Central Airway Dimensions and Air Trapping

A multidetector CT scanner (Aquilion 64; Toshiba, Tokyo, Japan) was used to acquire images using 0.5-mm collimation, a scan time of 500 ms, a peak of 120 kV, and auto-exposure control. Full-inspiratory (90% of VC) and full-expiratory (20% of VC) scans were acquired from the top to the bottom of the 2 lungs using a spirometric gating device (Fukuda Sangyo Co Ltd, Chiba, Japan).

Airway dimensions of the apical segmental bronchus of the right upper lobe were measured using customized software as described previously.[23] Luminal area (Ai) and absolute wall thickness (T) were measured automatically. The total diameter of the bronchus (D) was calculated as $D = 2\sqrt{Ai/\pi} + 2T$. The outer area of the bronchus (Ao) and airway-wall area (WA) were calculated as $Ao = \pi\,(D/2)^2$ and $WA = Ao - Ai$. The percentage of wall area (WA%) was calculated as $WA\% = (WA/Ao) \times 100$.

The percentage of a low-attenuation area (<−960 HU) to lung area (LAA%) and mean lung density (MLD) were calculated automatically.[24] LAA% and MLD were derived and averaged from 3 bilateral lung slices.[24] LAA% and MLD on inspiratory and expiratory scans and the ratios of these values at expiration to the respective values at inspiration (E/I ratios) were analyzed.

Statistical Analysis

JMP 6 (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. Results are presented as mean ± SD or median (range). To compare results before and after treatment, a paired *t* test or the