

PHARMCOTHERAPY

Effectiveness of Omalizumab in a Patient with Severe Asthma, Low Serum IgE Level, and Lack of Sensitized Allergens Induced by Oral Steroid Therapy: The Usefulness of Impulse Oscillation for Assessment of Omalizumab Therapy

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Background. Omalizumab is a humanized monoclonal anti-IgE antibody that was recently approved for the treatment of severe allergic asthma. However, omalizumab is not licensed for allergic asthma in patients with a low serum IgE level (<30 IU/mL) or negative results for specific allergen tests. **Case history.** We present a patient with severe asthma and low serum IgE levels who had negative results for specific allergens induced by oral steroid therapy. Omalizumab administration improved asthma exacerbated forced expiratory volume in 1 s (FEV_1) and respiratory resistance measurements based on the impulse oscillation technique (Mostgraph-01). The response to omalizumab therapy was evidenced by a decrease in airway resistance at 1 month. **Conclusions.** The findings of this case report indicate that omalizumab treatment had beneficial effects in a patient with severe asthma and low total serum IgE levels with negative results for specific IgE, which may have been induced by long-term corticosteroid administration.

Keywords impulse oscillation, lack of sensitized allergens, low IgE, Mostgraph-01, omalizumab

INTRODUCTION

Omalizumab is efficacious in the treatment of severe allergic uncontrolled asthma despite optimal therapy (1). Add-on omalizumab therapy is indicated for patients with a baseline total serum IgE level of 30–700 IU/mL and is administered every 2 or 4 weeks at a dose determined based on the body weight and total serum IgE level prior to treatment (1). In some groups, patients with severe persistent asthma have persistent low or high levels of total serum IgE (2). We report a patient with severe asthma with low IgE levels overall, who had low levels of specific IgEs, and who was treated successfully with omalizumab. Low levels of total serum IgE and negative results for specific IgEs may have been induced by oral corticosteroids.

Evans et al. (3) showed that when compared to spirometry, oscillometry was a more sensitive means of measuring changes in airway function. The effect of omalizumab has not been evaluated by oscillometry previously; therefore, we performed this analysis of omalizumab (Mostgraph-01) in addition to spirometry.

CASE STUDY

A 35 year-old nonsmoking, Japanese female was referred to our institution for management of difficult-to-control asthma. Her medical history was positive for allergic rhinitis and

dissociative disorder. She was diagnosed with allergic asthma in her childhood, but the asthma worsened after the age of 25 years. Treatment was gradually stepped up until she was eventually prescribed inhaled corticosteroids (budesonide, 640 μ g, two times; formoterol, 20 μ g, two times); oral montelukast 10 mg/day; oral betamethasone 0.5–1 mg, three times a day; and procaterol hydrochloride hydrate as needed, but her respiratory symptoms remained uncontrolled. The dissociative disorder did not affect her compliance with medication.

Her forced expiratory volume in 1 s (FEV_1) was 680 mL (28.5% of predicted) with a FEV_1 /forced vital capacity ratio 75.5% before treatment. FEV_1 reversibility with bronchodilators was not observed before omalizumab treatment. One month later, FEV_1 reversibility of 40.3% and 250 mL was observed. Her total serum IgE level was 2 IU/mL, without specific IgEs to any of the most common aeroallergens tested. Skin prick tests (SPTs) were also negative. Seven years before her presentation to our clinic, her total serum IgE level was 440 IU/mL and positive for house dust and mites.

Because the patient had a high total serum IgE level and was positive for specific IgEs before treatment with oral corticosteroids, we hypothesized that she might benefit from omalizumab treatment, despite her present status of low total serum IgE levels and a lack of sensitization to exogenous allergens. The patient was treated once a month with 150 mg omalizumab injected subcutaneously. She exhibited a gradual improvement in her symptoms and in the frequency of her asthma attacks. Her Asthma Control Test (ACT) score at the initial evaluation was 6. After omalizumab treatment, the ACT rose to 10 after 3 months, then 17 after 6 months.

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Compared with the previous 6 months, the number of emergency room visits and steroid infusions decreased from 2 to 0 and from 20 to 5, respectively.

Spirometry and impulse oscillation (Mostgraph-01, CHEST, Tokyo, Japan) tests were performed monthly from before to after 24 weeks of the treatment. The Mostgraph-01 was recently developed in Japan and it enables total respiratory resistance (Rrs) measurements of airways by impulse oscillation or pseudorandom noise, as well as evaluations of respiratory system elasticity (4, 5). The Mostgraph-01 system provides simultaneous measurements of multiple frequencies and features the ability to track changes over time within breathing cycles. The results are shown in 3D color graphs (Figure 1).

FEV₁ and resistance at 5 Hz (R5) improved from 0.68 L and 10.00 cmH₂O/L/s, respectively, before treatment to 1.03 L and 5.68 cmH₂O/L/s, respectively, 6 months after omalizumab treatment. In particular, the response to omalizumab therapy was evidenced by the decrease in airway resistance 1 month after the beginning of omalizumab treatment (Figure 2).

Many patients with severe persistent asthma have low or high levels of total serum IgE. Some patients with severe asthma and elevated total serum IgE levels have negative radioallergosorbent and SPT results (6, 7). The different phenotypes of asthma have several similarities, with similar cytokine and cellular patterns in both allergic and nonallergic asthma (8, 9). Ying et al. (10) demonstrated increases in

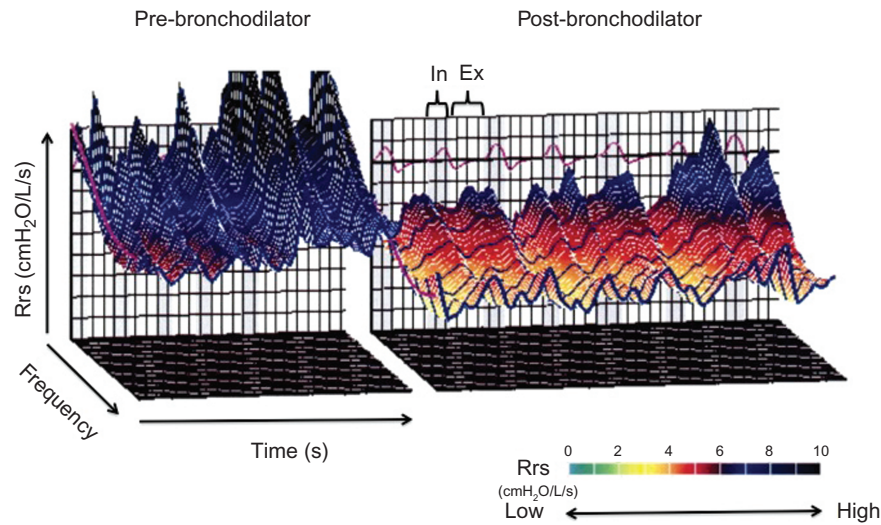


FIGURE 1.—Three-dimensional graphs of respiratory resistance (Rrs) at baseline before treatment with omalizumab and the response to the bronchodilator Salbutamol (20 min later). In, inhalation; Ex, exhalation.

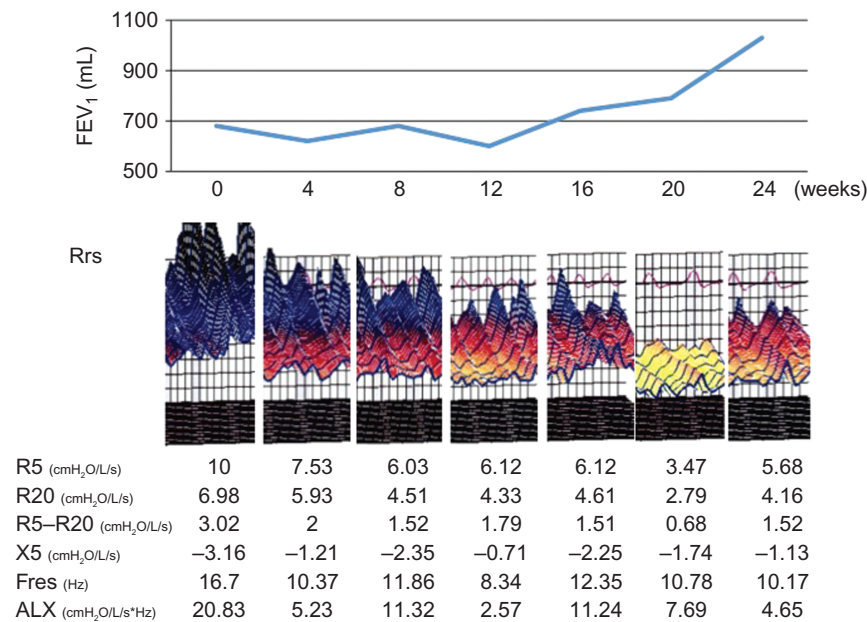


FIGURE 2.—Changes in R5, R20, R5-R20, X5, Fres, ALX, and FEV₁ over time are shown after omalizumab treatment. 3D graphs of respiratory resistance (Rrs) are also displayed. R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz; Fres, resonant frequency; ALX, low-frequency integrated reactance.

I-epsilon and C-epsilon RNA(+) cells, but not B-cell numbers, in the bronchial mucosa, indicating local IgE synthesis in both atopic and nonatopic asthma. Therefore, IgE may have a key role in the inflammatory cascade (even in the absence of a proven aeroallergen), contributing to bronchial hyperreactivity and remodeling in asthma. Higher serum IgE values are associated with higher bronchial hyperreactivity and more severe obstruction (11). Naqvi et al. (12) reported on total IgE-related asthma severity in African American, Mexican, and Puerto Rican patients with asthma. Total IgE is associated with asthma severity in those patient populations.

A sub-analysis of data from a large multicenter study demonstrated that omalizumab is less beneficial for patients with total serum IgE levels of 0–75 IU/mL, even for those testing positive for perennial allergen-specific IgE (13). In contrast, Wahn et al. (15) and Bousquet et al. (14) reported that response to omalizumab is not predicted by total IgE. Ankerst et al. (16) reported that omalizumab is effective for patients with severe asthma with a low total serum IgE level and positive for SPT and allergen threshold sensitivity.

It is currently unknown whether omalizumab has a beneficial effect in patients with allergic asthma without elevated total serum IgE levels or positivity for specific antigens induced by oral corticosteroid administration. In this case study, treatment with omalizumab was successful for a patient who had an IgE concentration of 2 IU/mL and negative results for radioallergosorbent test (RAST) tests. In such patients, the use of high-dose corticosteroids may suppress IgE production to some degree. It is likely that IgE levels will rise when these therapies are reduced.

Chronic steroid use (higher than 20 mg daily) can partially suppress SPT reactions (17). Short-term (<1 week) administration of corticosteroid at therapeutic doses in asthmatics does not modify SPT (18). Conversely, long-term steroid treatment does not alter histamine-induced vascular reactivity in skin but affects skin mast cell response. Long-term steroid treatment decreases the number of mast cells in the skin (17).

This is the first report of the effectiveness of omalizumab based on impulse oscillometry. Evans et al. (3) reported that impulse oscillometry was a more sensitive means of measuring changes in airway function than spirometry, although there are no reported cases of the effect of omalizumab evaluated by oscillometry. The Mostgraph-01 was developed recently and is useful for assessing the oscillatory mechanics of the respiratory system (4, 5). The display of results is different from those of impulse oscillometry system (IOS). In this case study, the response to omalizumab therapy was evidenced by a decrease in airway resistance 1 month after the beginning of treatment, although FEV₁ was not improved. It is possible that the response to omalizumab is detected by impulse oscillometry earlier than by spirometry.

CONCLUSION

Taken together, the findings of this case report indicate that omalizumab treatment had beneficial effects in a patient with severe asthma and low total serum IgE levels

with negative results for specific IgE, which may have been induced by long-term corticosteroid administration. Further studies are needed to identify a new indicator for clinicians to determine which asthmatic patients might respond to omalizumab, even if their total serum IgE levels are low and they have negative results for allergen-specific IgEs. Oscillometry versus FEV₁ changes were very interesting and would warrant further studies.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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