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REVIEW ARTICLE

Anti-IgE Antibody Therapy for Japanese Cedar Pollinosis: Omalizumab Update

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ABSTRACT

Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollens is a substantial problem in Japan. Omalizumab, a novel humanized monoclonal anti-immunoglobulin E (IgE) antibody, has already been proven to reduce symptoms associated with SAR. To investigate the safety and efficacy of omalizumab in the treatment of patients with Japanese cedar pollen-induced SAR compared to placebo or anti-allergic drug, two randomized, double-blind studies were conducted in Japan. Omalizumab (150, 225, 300, or 375 mg) or placebo was administered subcutaneously every 2 or 4 weeks based on serum total IgE and body weight at baseline. IPD was administered 300 mg per day through the season. Primary and all secondary efficacy variable scores were significantly lower in the omalizumab group than in the placebo group ($P < .01$) and IPD, Th2 cytokine inhibitor group ($P < .01$). Omalizumab was effective and safe in the treatment of SAR induced by Japanese cedar pollens. And the methods of increasing effects by combining omalizumab with antibody-specific immunotherapy are being considered. These strategy is more effective than immune-therapy alone.

KEY WORDS

anti-IgE therapy, asthma, immunotherapy, omalizumab, seasonal allergic rhinitis

INTRODUCTION

Allergic rhinitis including hay fever is a disorder in which sensitization occurs through the inhalation of antigens (induction phase), and a local immune reaction then takes place between the antigen-specific IgE thereby produced and the antigens which have invaded the nasal mucosa (effecter phase). Treatment for allergic rhinitis depends on suppressing the flow of this allergic reaction at some point. Antigen-specific immunotherapy has its point of effect earlier than midway between the induction phase and effecter phase of allergic reaction, unlike general allergy medications (antihistamines, chemical mediator release inhibitors, leukotriene receptor antagonists, etc.). The anti-IgE antibody omalizumab is also such a drug whose point of action differs from previous allergy medications.

THE KNOWLEDGE OF ANTI-IgE ANTIBODY THERAPY

The anti-IgE antibody (omalizumab) produces its effect by binding to IgE which is not bound to mast cells, inhibiting it from binding to mast cells. Since omalizumab does not affect T cells, unlike conventional immunotherapy it is not a curative therapy, but it is a groundbreaking drug in its application of an immunological concept.[1]

This drug is under application in Japan as indicated for severe asthma. There is certainly much evidence for asthma and this is good news for inadequately controlled asthma. In the field of asthma the concept of response to omalizumab has already been published.[2] Currently research is focused on cost-effectiveness. Medical expenses for asthma in America in 2002 (direct and indirect expenses) totaled 14 billion dollar (direct medical expenses: 3.1 billion dollar for hospitalization, 4.6 billion dollar for drugs). The cost of omalizumab to improve QOL is 821,000 dollars, and at present cost-effectiveness is not good. If it could be reduced to 200 dollars or less, it is calculated that cost-effectiveness would increase.[3] However, in correspondence, D. Revicki argues that the purely medical cost-effectiveness which is not based

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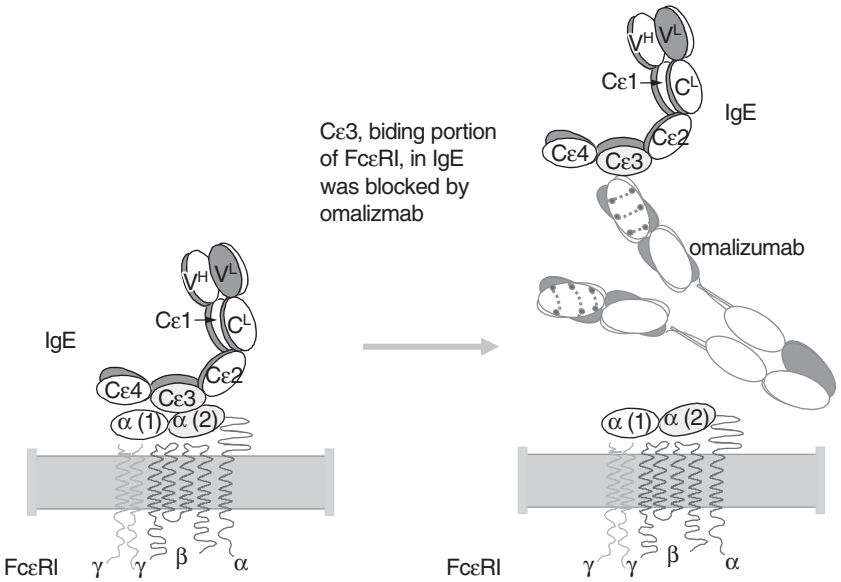

Fig. 1 The inhibition mechanism of allergic disease by omalizumab. Omalizumab was humanized monoclonal antibody against C epsilon 3 portion of Fc epsilon receptor I. Omalizumab blocks the binding between IgE and Fc epsilon receptor I, so allergic symptom must be reduced by this mechanism.

on the Asthma Policy Model is better.[4] The cost-effectiveness will be a large issue in using omalizumab for all allergic disorders in the future.

ANTI-IgE ANTIBODY

In 1991, the American company Genentech produced an antibody specific to Cε3 that binds to Fcε receptors, in the constant region of human IgE. Omalizumab is a humanized monoclonal antibody using mouse monoclonal antibody as a base, retaining the antigen-specific region and replacing the other fragments with human IgGlκ.

When this antibody binds to free IgE in blood by an antigen-antibody reaction between the Fcε receptor and the Cε3 binding site, an IgE–anti-IgE complex is formed, and as a result, free IgE is decreased (Fig. 1). Therefore, IgE that binds to mast cells is decreased, so that even if antigens invade, binding to mast cells to form cross-linking is inhibited and allergic reaction is controlled. Another effect is to inhibit the differentiation of B cells into IgE-producing cells. This is thought to be because it reacts with membrane-binding IgE on B cells, inhibiting mRNA expression of the ε chain. In actual animal experiments, IgE-producing B cells are virtually eliminated.[5]

EFFECTS OF ANTI-IgE ANTIBODY THERAPY IN THE US AND EUROPE

In the West, clinical trials of anti-IgE antibody therapy using omalizumab have been conducted for several years by subcutaneous injection. The target disorders are allergic rhinitis and atopic asthma, and clinical trials are being conducted in Japan for the same targets. In the West, the trials for hay fever differ from asthma, being conducted at single doses of 150 mg or 300 mg. Casale *et al*. have reported on a double-blind comparative trial of those dose levels plus a placebo and 50 mg for a total of 4 groups, using American patients with ragweed pollinosis.[6] The condition of 300 mg group was better than the placebo group throughout the pollen dispersal season and at the peak of pollen dispersal. Lower dose levels also showed effects, and dose relationship was observed. Omalizumab also showed significant improvement by the RQLQ (Juniper's QOL questionnaire). Similar results have been obtained for birch pollinosis in the West, and reduction in drugs for emergency use is being evaluated (Fig. 2).[7]

EFFECTS ON JAPANESE CEDAR POLLINOSIS IN JAPAN

Clinical trials were conducted on Japanese cedar pollinosis in Japan in 2002 and 2003. The trials of 2002 and 2003 were placebo-controlled comparative study and comparative study with an anti-allergy drug, respectively.

The placebo-controlled study used a dose concept of considering the level of omalizumab which can eliminate IgE systemically, as with asthma in Japan, in contrast to the overseas studies which have a set dosage of 300 mg. The amount of omalizumab was set from body weight and IgE level immediately before administration in December as 0.0016 mg/kg/

IgE (IU/mL) and revised every 4 weeks. Therefore, IgE was uniformly reduced to the detection limit (50 ng/mL) in the administration group. Results of the study showed omalizumab significantly reduced the nasal symptom medication score by about 40% for e, and significantly reduced ocular symptoms by 50% (Fig. 3). Individual symptoms of Japanese cedar pollinosis (itchy nose, sneezing, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes) were all significantly alleviated (Fig. 4). Both nasal and ocular symptoms were decreased significantly more than in the placebo group. The major adverse event was pain at the injection site. And one case of ulcerative colitis was reported, but the colitis manifestation is not thought to be responsible omalizumab application.[8]

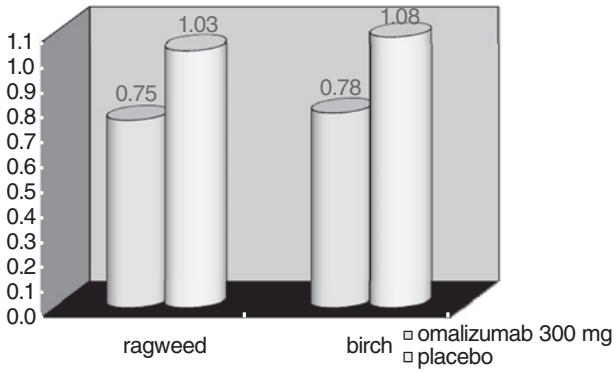

Fig. 2 Overseas study of omalizumab for ragweed or birch pollinosis. Daily nasal severity score in the placebo controlled study of the patients with ragweed pollinosis (reference 6), and birch pollinosis (reference 7). Significant reduction of daily nasal severity score in omalizumab group (yellow bar) compared to that in placebo (purple bar) at both studies.

In 2003, an active control study was conducted with IPD, Th2 cytokine inhibitor. Because the results of the placebo-controlled study were satisfactory, the first active control study, double dummy comparative controlled trial, of omalizumab in the worldwide was conducted. Dose levels were set to compare omalizumab and IPD using the dose concept. 300 mg per day of IPD was administered initial treatment from beginning of February, and through the season. The nasal symptom medication score during the pollen dispersal season was 30% lower than IPD (Fig. 5). In individual symptoms, omalizumab was more effective than IPD for sneezing, runny nose and stuffy nose, although there were no significant differences in itchy nose or ocular symptoms. Omalizumab was more effective to the same degree through the pollinating season including the high pollen dispersal season, and there were no adverse reactions.[9]

Omalizumab is currently under application at the Ministry of Health, Labour and Welfare for severe asthma, but application for hay fever has not been made. This may be because it is not a life-threatening illness, and since there are many patients, recogni-

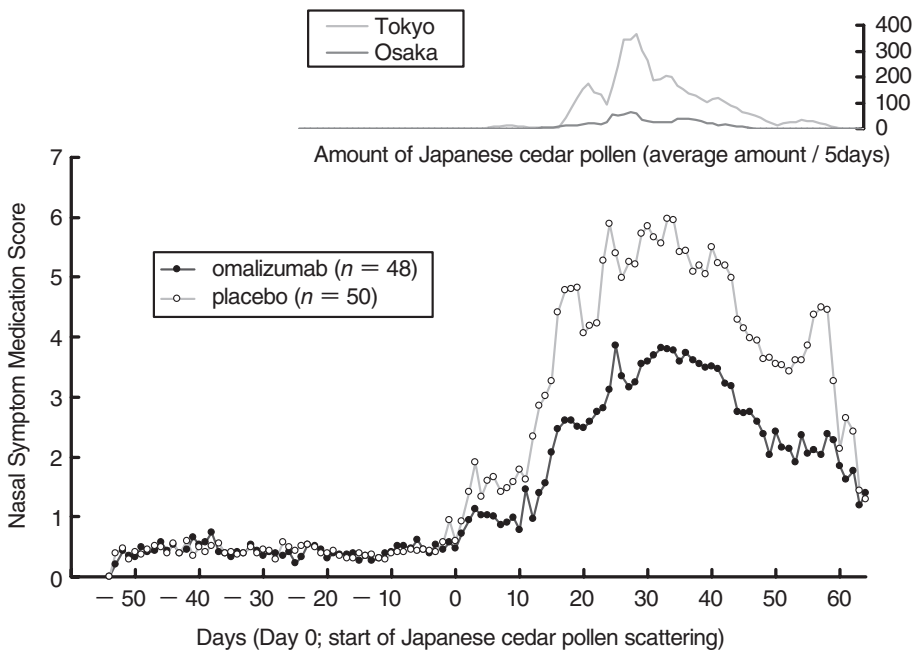

Fig. 3 The change in daily nasal symptom medication score in patients with Japanese cedar pollinosis in 2002. The nasal symptom medication score was significantly reduced in omalizumab group (filled square) in Japanese cedar pollen dispersing season in Tokyo and Osaka compared to the score in placebo (open square).

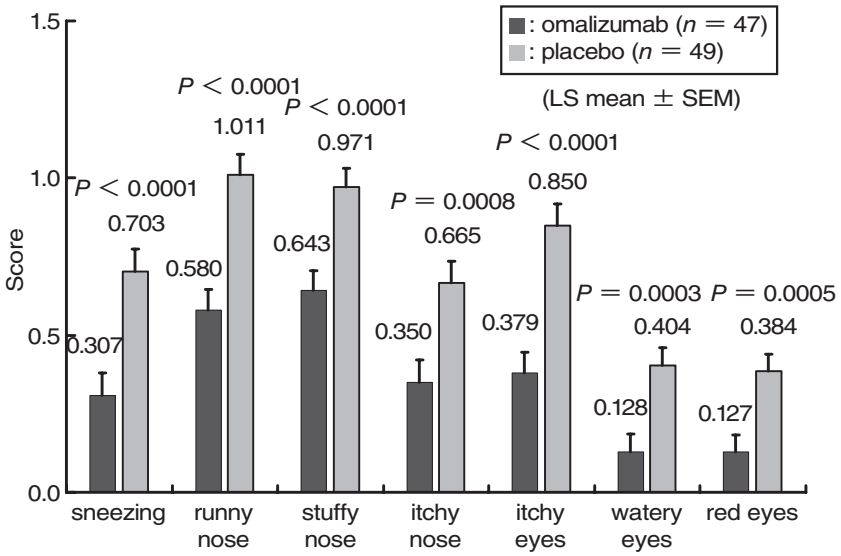

Fig. 4 The change in daily nasal and ocular symptom score in patients with Japanese cedar pollinosis in 2002. All symptoms score, sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes, were significant reduced in omalizumab group (purple bar) compared with the score in placebo (yellow bar), especially in eye symptoms.

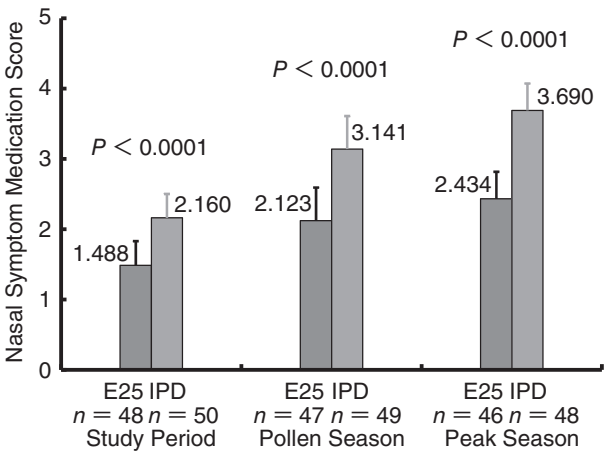

Fig. 5 The daily nasal symptom medication score in comparative study between omalizumab (E25) and IPD for patients with Japanese cedar pollinosis in 2003. Nasal symptom medication score was evaluated in three periods such as study period, pollen dispersing period (pollen season), peak pollen dispersing period (peak season). In all three period, nasal symptom medication score with omalizumab (E25) group (grey bar) was reduced compared to the score with the placebo (orange bar).

tion of the indication could lead to improper use. At any rate, application for allergic rhinitis, including Japanese cedar pollinosis has not been made in any country, but if with advances in technology lower costs for antibody manufacturing and means of reduction to safer numbers can be attained, the treatment for hay fever will become broader in Japan in the future.

OTHER USES FOR ANTI-IgE THERAPY

Overseas, methods of increasing effects by combining omalizumab with antibody-specific immunotherapy are being considered. Wahn *et al.* conducted an RCT in children with sensitization to birch and grass pollen using immunotherapy for either in combination with omalizumab, and the symptom scores for each immunotherapy were further reduced by half.[10] In a study of the same group, leukotriene release by antigen stimulation after the pollen dispersal season that was not reduced by immunotherapy alone was suppressed. However, this suppression reverts back one month after treatment.[11] Klunker *et al.* described combination with rush immunotherapy against ragweed pollinosis. In this study omalizumab administration was begun 9 weeks before the start of rush immunotherapy, with improved effects. This idea is in accordance with the idea of administering omalizumab before the advent of symptoms in the Japanese clinical study. There were no differences in the symptom scores of omalizumab alone and rush immunotherapy combined with omalizumab, but the ability of B cells to bind with allergen-IgE complexes was inhibited more than by rush immunotherapy alone. That is, omalizumab was shown to inhibit CD23 expression in B cells for 30 weeks after completion of immunotherapy at week 42.[12]

A study on nasal polyps was also conducted. Penn

et al. performed endoscopic surgery on nasal polyps complicated by allergic asthma and allergic rhinosinusitis, and observed the course of omalizumab administration thereafter. Recurrence was 25% with and without omalizumab (1/4), but the number of cases was small, and the effects have not been completely verified.[13,14]

THE FUTURE

In the field of allergies there are few illnesses in which IgE does not play a role, and the time may be coming when the use of omalizumab will be considered for all disorders whose pathology has some involvement of IgE. There are many problems that need to be overcome, including that of cost. However, as it is, reduction of IgE can improve the clinical condition in almost all allergic disorders, and we must demonstrate in Japan as well that the current application of omalizumab can be expanded to other indications.

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