



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Invited Review Article

Roles of omalizumab in various allergic diseases

Yoshimichi Okayama^{a, b, c, **, 1}, Hisako Matsumoto^{d, *, 1}, Hiroshi Odajima^{e, ***, 1}, Shunsuke Takahagi^{f, 1}, Michihiro Hide^{f, ***, 1}, Kimihiro Okubo^{g, ****, 1}^a Allergy and Immunology Research Project Team, Research Institute of Medical Science, Nihon University School of Medicine, Tokyo, Japan^b Center for Allergy, Nihon University Itabashi Hospital, Tokyo, Japan^c Center for Medical Education, Nihon University School of Medicine, Tokyo, Japan^d Department of Respiratory Medicine, Graduate School of Medicine Kyoto University, Kyoto, Japan^e Department of Pediatrics, National Hospital Organization Fukuoka National Hospital, Fukuoka, Japan^f Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan^g Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan

ARTICLE INFO

Article history:

Received 25 December 2019

Available online xxx

Keywords:

Childhood asthma

Chronic urticaria

Omalizumab

Severe allergic asthma

Severe pollinosis

ABSTRACT

IgE and mast cells play a pivotal role in various allergic diseases, including asthma, allergic rhinitis, and urticaria. Treatment with omalizumab, a monoclonal anti-IgE antibody, has significantly improved control of these allergic diseases and introduced a new era for the management of severe allergic conditions. About 10 years of experience with omalizumab treatment for severe allergic asthma confirmed its effectiveness and safety, reducing symptoms, frequency of reliever use, and severe exacerbations in patients with intractable conditions. Omalizumab is particularly useful in childhood asthma, where atopic conditions often determine clinical courses of asthma.

Recently, omalizumab is approved for the treatment of chronic spontaneous urticaria (CSU) with the fixed dose of 300 mg. Although the mechanisms underlying the actions of omalizumab in CSU are not fully clarified, nearly 90% of patients with CSU showed a complete or a partial response to omalizumab treatment. Furthermore, omalizumab is just approved for the treatment of severe Japanese cedar pollinosis (JC) based on the successful results of an add-on study of omalizumab for inadequately controlled severe pollinosis despite antihistamines and nasal corticosteroids. For proper use of omalizumab to treat severe JC, co-administration of antihistamines is necessary, while patients should meet the criteria including strong sensitization to Japanese cedar pollen ($\geq$ class 3) and poor control under standard treatment.

In the management of severe allergic diseases using omalizumab, issues including cost and concerns about relapse after its discontinuation should be overcome. At the same time, possibilities for application to other intractable allergic diseases should be considered.

Copyright © 2020, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author. Department of Respiratory Medicine, Kyoto University, 54 Kawaharamachi, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

** Corresponding author. Allergy and Immunology Research Project Team, Research Institute of Medical Science, Center for Allergy, Center for Medical Education, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan.

*** Corresponding author. Department of Pediatrics, National Hospital Organization Fukuoka National Hospital, 4-39-1, Yakatabaru Minami-ku, Fukuoka 811-1394, Japan.

**** Corresponding author. Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

***** Corresponding author. Department of Otorhinolaryngology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.

E-mail addresses: okayama.yoshimichi@nihon-u.ac.jp (Y. Okayama), hmatsumo@kuhp.kyoto-u.ac.jp (H. Matsumoto), odajima.hiroshi.uk@mail.hosp.go.jp (H. Odajima), ed1h-w1de-road@hiroshima-u.ac.jp (M. Hide), ent-kimi@nms.ac.jp (K. Okubo).

Peer review under responsibility of Japanese Society of Allergology.

¹ All authors contributed equally to this manuscript.

<https://doi.org/10.1016/j.alit.2020.01.004>

1323-8930/Copyright © 2020, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The discovery of IgE by Professors Kimishige and Teruko Ishizaka has had a significant effect on the diagnosis and management of allergic diseases. About 40 years later, a monoclonal anti-IgE antibody, omalizumab, has been developed and opened a new era against various severe allergic diseases. Omalizumab has been first approved for in Australia (2002) followed by the United States (2003), the European Union (2005), and Japan (2009), first for severe uncontrolled asthma in adults and then in children. More recently, omalizumab is applied for the treatment of chronic spontaneous urticaria (CSU) with successful outcomes and has just been authorized for severe Japanese cedar pollinosis (JC). In this review, we provide an overview of the mechanisms of action and effectiveness of omalizumab against major IgE related diseases; adult and childhood severe allergic asthma, CSU, and severe JC.

Basic mechanisms of omalizumab

Structure and receptor interactions of IgE

The shape of the IgE molecule differs dramatically from that of IgG. Specifically, the (Cε2)₂ domain pair is folded back against the Cε3 and Cε4 domains.^{1,2} IgE binds to allergens through their Fab arms and expresses their effector functions by binding to receptors for the (Cε3)₂ domain of the Fc region (Fig. 1A). The two principal IgE receptors are FcεRI and CD23/FcεRII, commonly referred to as the high-affinity ($K_D \approx 10^{-10}$ M) and the low-affinity ($K_D \approx 10^{-7}$ M) receptors, respectively. Conformational changes occur upon the binding of IgE to FcεRI on mast cells, basophils and antigen-presenting cells. CD23 is a homo-trimeric type-II membrane protein with its C-terminal C-type lectin-like “head” domains, to which IgE binds, spaced from the membrane by a triple α-helical coiled-coil “stalk” (Fig. 1B).^{3,4} A disintegrin and metalloproteinase 10 (ADAM10), which is an endogenous protease, releases soluble CD23.^{5,6} IgE also binds to galectin-3 and several co-receptors for CD23, notably CD21 and various integrins.⁷

Function of IgE

Mast cells and basophils are sensitized with pre-bound IgE, requiring only the presence of an allergen to cross-link IgE/FcεRI complexes and elicit an immediate reaction that involves mast-cell degranulation and the synthesis of lipid mediators (Fig. 2A). Cytokines and chemokines are produced some hours later following the aggregation of FcεRI and induce the recruitment and activation of inflammatory cells at sites sensitive to the allergen. IgE binds to FcεRI on the surface of Langerhans cells and epithelial dendritic cells. Following the capture of allergens, they either migrate to local lymph nodes or possibly remain in the tissues where they present the processed allergens to T_H2 cells (Fig. 2B).⁷ CD23 plays several important roles in allergic inflammation. CD23 is a key molecule in IgE-facilitated allergen presentation and the subsequent activation of allergen-specific T cells (Fig. 2C).^{8,9} Furthermore, CD23 is thought to be important in the regulation of IgE production.¹⁰ The positive regulation of IgE synthesis is a result of the co-ligation of membrane IgE-B cell receptor [BCR] and CD21 on a human B cell committed to IgE synthesis by soluble CD23 released from membrane-bound CD23 (Fig. 2D).⁷ The negative regulation of IgE synthesis occurs as a result of the co-ligation of IgE and CD23 on the membrane by allergen–IgE complexes (Fig. 2E).¹¹ CD23 mediates the transcytosis of IgE/allergen complexes through respiratory and gut epithelial barriers.^{12,13} This mechanism allows the delivery of intact complexes to mast cells in the gastrointestinal mucosa, where they can trigger food allergy reactions. Thus, IgE-receptor interactions are involved in multiple aspects of the allergic response, and IgE is a long-standing target for therapeutic intervention.

Mechanisms of regulatory effect of omalizumab on allergic inflammation

Omalizumab is a humanized IgG1κ monoclonal antibody that specifically binds to the Cε3 domain of the Fc region of human IgE in blood and interstitial fluid, thereby binding to free IgE and as well as the membrane-bound form of IgE (mIgE; IgE- BCR) on the surface of mIgE-expressing B lymphocytes.¹⁴ Omalizumab, a clinically

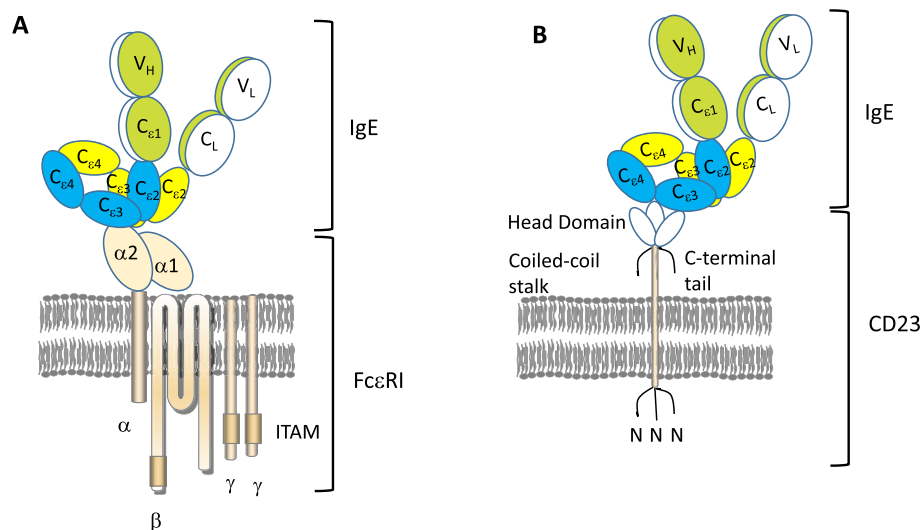


Fig. 1. Structure of the FcεRI α-chain (A), CD23 (B) and its complex with IgE. (A) Schematic representation of the entire IgE molecule bound to the extracellular domains of the FcεRI α-chain, according to the structural information from the Fcε3-4 complex and the bent IgE-Fc structure. The β- and γ-chains of FcεRI, along with their immunoreceptor tyrosine-based activation motifs (ITAMs), are also shown. (B) Schematic representation of the entire IgE molecule bound to the membrane-bound CD23, showing the extracellular trimeric α-helical coiled-coil “stalk,” the three C-type lectin domain “heads,” and the C-terminal “tails.”

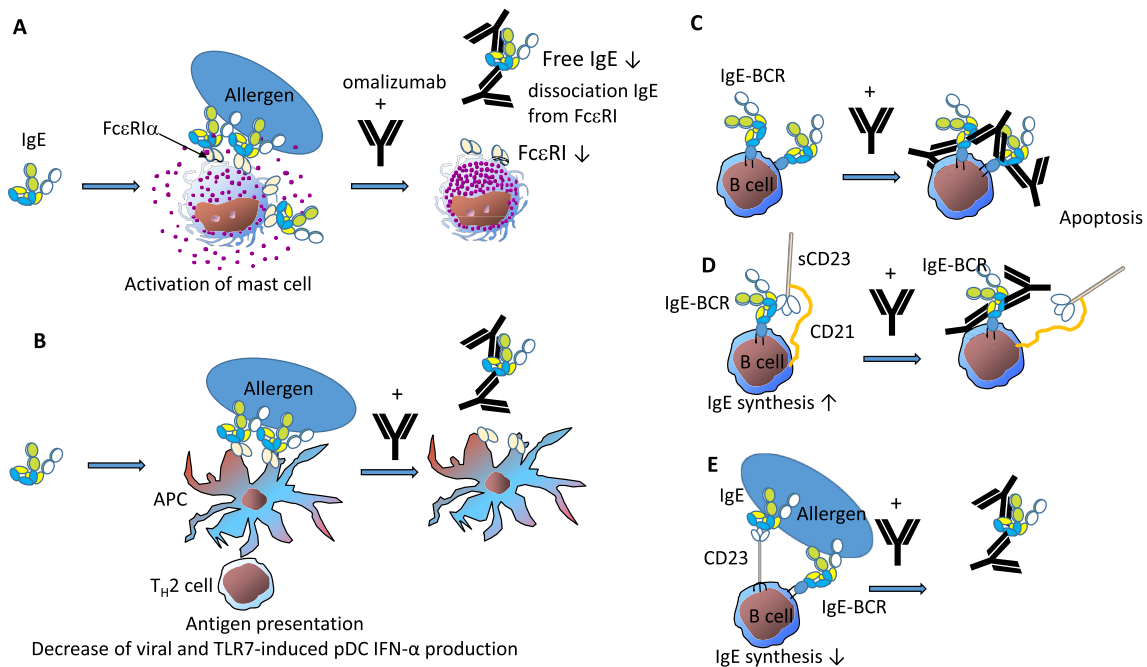


Fig. 2. Mechanisms of inhibitory effect of omalizumab on allergic inflammation. (A) IgE binds to FcεRI on mast cells and antigen-presenting cells (APCs). IgE sensitizes these cells to the allergens. Omalizumab inhibits the binding of IgE to FcεRI on mast cells and APCs. (B) Omalizumab can actively dissociate IgE from FcεRI. (C) Omalizumab shows a pronounced crosslinking activity with BCR in an inducible IMIGEC (acronym for inducible membrane IgE clone) cell reporter system,¹⁶ suggesting that omalizumab provides apoptotic signals. (D) The positive regulation of IgE synthesis is a result of the co-ligation of membrane IgE-BCR and CD21 on a human B cell committed to IgE synthesis by soluble CD23 released from membrane-bound CD23. Omalizumab inhibits the binding of IgE-BCR to CD23. (E) The negative regulation of IgE synthesis occurs as a result of the co-ligation of IgE and CD23 on the membrane by allergen-IgE complexes. Omalizumab inhibits the binding of IgE to CD23. pDCs, plasmacytoid dendritic cells; TLR, toll-like receptor.

approved therapeutic antibody, inhibits the interaction between IgE and FcεRI and markedly decreases levels of free IgE in circulation, resulting in a reduction in the expression of FcεRI (Fig. 2A).

Omalizumab might also contribute to IgE suppression by targeting the IgE-BCR on IgE-switched B cells.¹⁵ In the absence of T helper signals, crosslinked membrane IgE-BCR provides apoptotic signals and/or might mediate antibody-dependent cellular cytotoxicity, both of which would eventually suppress the IgE supply by depleting IgE-switched B cells (Fig. 2C). Omalizumab showed a pronounced crosslinking activity with BCR in an inducible IMIGEC (acronym for inducible membrane IgE clone) cell reporter system used for the quantitative assessment of IgE BCR crosslinking activity.¹⁶

The crystal structure of the complex between an omalizumab-derived Fab and IgE-Fc, with one Fab bound to each Cε3 domain, was analyzed.¹⁷ The structure reveals two molecules in complex with IgE-Fc, one bound to each of the two Cε3 domains, and provides an explanation for the ability of omalizumab to inhibit the binding of IgE to both FcεRI and CD23.¹⁸ The stalk region of CD23 is crucially involved in IgE binding, and this interaction can be blocked by omalizumab.¹⁸ IgE-Fc can also adopt a partially bent conformation in the complex.¹⁷ Omalizumab can actively dissociate IgE from FcεRI, albeit at concentrations higher than those used therapeutically¹⁹ by utilizing allostery and the intrinsic flexibility of IgE that persists even when in complex with its receptors.¹⁷

Atopy and viral respiratory tract infections synergistically promote asthma exacerbations. The surface expression of FcεRI on plasmacytoid dendritic cells (pDCs) is significantly correlated with serum IgE concentrations²⁰ and is associated with diminished virus-induced IFN-α responses in these cells.²¹ The magnitude of pDC IFN-α responses to an *ex vivo* viral challenge is inversely related to the serum IgE levels,²⁰ and stimulation of the IgE/FcεRI pathway in pDCs through IgE cross-linking abrogates viral and Toll-

like receptor 7-induced pDC IFN-α production (Fig. 2B).^{20,22} The pDCs isolated from patients with allergic asthma exhibit impaired IFN-α responses to viruses. Omalizumab treatment augments these pDC IFN-α responses and attenuates pDC FcεRIα protein expression.²³

Role of omalizumab in severe allergic adult asthma

Efficacy of omalizumab in severe allergic adult asthma

Omalizumab is the first biologic that was globally approved for the treatment of severe or moderate to severe allergic asthma, which is administered subcutaneously every two or four weeks at a dose determined according to the patient's body weight and serum total IgE levels (30–1500 IU/mL), ranging from 75 to 600 mg. Omalizumab exerts a number of effects,²⁴ including improvement in quality of life (QOL) and pulmonary function and reduction in asthma symptoms, asthma exacerbations, and doses of ICS. Oral corticosteroid doses were also reduced after omalizumab treatment in several studies. A meta-analysis of eight randomized controlled studies showed that omalizumab decreased severe asthma exacerbations by 43%.²⁵ Using the Global Evaluation of Treatment Effectiveness, a meta-analysis of 25 real-world studies revealed that 77% of patients with severe asthma experienced remarkable or moderate improvement four to six months after starting omalizumab treatment.²⁶ A study conducted on an Asian population showed a significant increase in morning peak flow after 16 weeks of omalizumab treatment, as well as a 68% decrease in the frequency of exacerbations when compared with that in pre-treatment.²⁷ Recent real-world study from Japan confirmed safety and efficacy of omalizumab with improvement in 62% of patients at 52 weeks.²⁸ Furthermore, omalizumab treatment may improve airway remodeling.^{29–31}

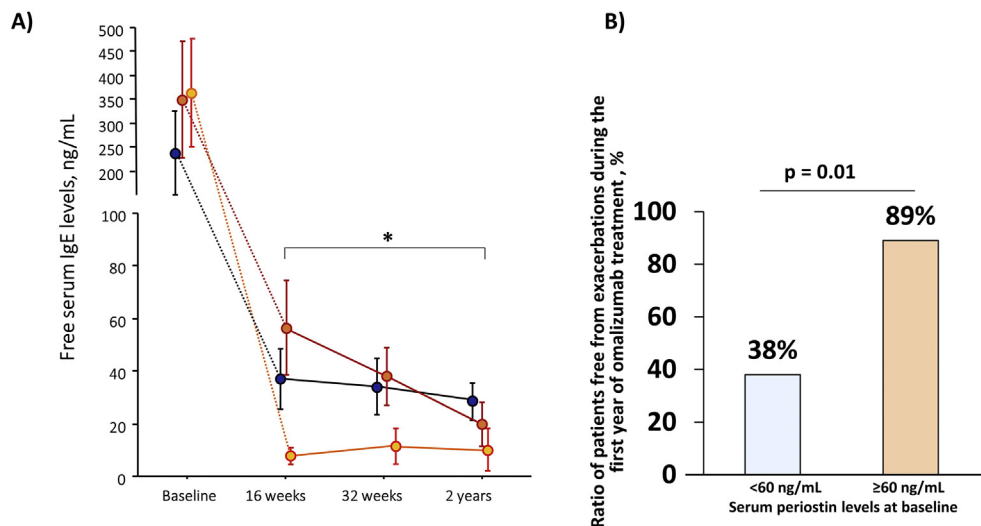


Fig. 3. Effects of omalizumab treatment on serum free IgE levels (A) and exacerbations (B) in adult patients with allergic asthma. (A) Average serum free IgE levels monitored over 2 years of omalizumab treatment in patients who still experienced asthma exacerbations during the first year of omalizumab treatment (red circle; * $P < 0.001$ by repeated-measures analysis of variance), those who experienced asthma exacerbations 1 year before but not 1 year after omalizumab treatment (orange circle), and those who did not experience asthma exacerbations both pre- and post-omalizumab treatment (blue circle) are shown.³² (B) The proportions of patients free from asthma exacerbations one year after omalizumab treatment stratified according to baseline serum periostin levels are presented.³⁹

Following omalizumab initiation, serum free IgE dramatically decreases, subsequently reaching its target levels (less than 25–50 ng/mL) in most cases (Fig. 3A).^{32–35} A decline in serum free IgE levels from baseline to 16 or 32 weeks after treatment was associated with reduced exacerbation frequency 2 years after omalizumab treatment.³² A study involving omalizumab discontinuation after 28 weeks of treatment showed that suppressed free IgE levels returned to baseline within 18–20 weeks, which was accompanied with re-emergent of asthma symptoms.³³

The efficacy of omalizumab may not attenuate even after long-term treatment, based on a study that examined the efficacy over 4 to 6, 12, and 24 months of treatment. As for the possibility of discontinuation of omalizumab treatment, after an average of 22.7 ± 13.1 months of treatment, 55.7% developed loss of asthma control within a median interval of 13 months.³⁶ A prospective study on persistency of omalizumab response after long-term omalizumab treatment showed that 72.9% of patients who continued omalizumab treatment were free from asthma exacerbations during the following year, whereas only 53.5% of patients who discontinued omalizumab treatment experienced the same.³⁷

Responses to omalizumab treatment in atopic eosinophilic and atopic non-eosinophilic patients

Original omalizumab trials did not enroll an enriched population, which is different from recent trials on anti-IL-5 class biologics. Nonetheless, *post-hoc* studies suggest that the efficacy of omalizumab may be greater in more enriched population with high type 2 biomarkers. The EXTRA omalizumab study had reported that patients with higher levels of FeNO, blood eosinophils, and serum periostin at baseline were more responsive to omalizumab treatment than those with lower levels thereof in terms of the reduction in asthma exacerbations during the first year of treatment.³⁸ We confirmed this, showing that higher FeNO levels were the best predictive marker of improvement in asthma control 16 weeks after treatment and that higher serum periostin levels were the best predictive marker of reduction in severe exacerbations 1 year after omalizumab treatment (Fig. 3B).^{32,39} A recent study that used patient enrichment criteria from omalizumab trials confirmed that

higher baseline blood eosinophil levels were related to greater reductions in exacerbation rates 16 weeks after omalizumab treatment.⁴⁰ This study also showed that patients with more frequent history of emergency asthma treatment, severer airflow limitation, and higher daily doses of ICS showed greater reduction in exacerbation rates after omalizumab treatment. Meanwhile, the presence of severe type 2 inflammation may hinder the successful discontinuation of omalizumab treatment. After long-term omalizumab treatment, patients who experienced asthma exacerbations after discontinuation showed higher blood eosinophil counts than those who were free from exacerbations.³⁷ Some atopic patients with early onset asthma do not show prominent eosinophilic/type 2 inflammation, so that they might be categorized into poor responders. However, they slowly respond to omalizumab treatment with the gradual decrease in serum free IgE levels after a 2-year follow-up (Fig. 3A).³²

Role of omalizumab in severe asthma comorbidities

Aspirin-exacerbated respiratory disease (AERD)

AERD is characterized by a triad of asthma, eosinophilic rhinosinusitis with nasal polyposis, and cysteinyl leukotriene overproduction. Mast cell activation and the interaction between platelets and granulocytes are involved in the pathobiology of AERD. Hayashi *et al.* revealed that omalizumab treatment reduced daily oral corticosteroid doses and frequency of asthma exacerbations in patients with AERD with significant reduction in urinary concentrations of leukotriene E_4 and prostaglandin D_2 metabolite.⁴¹ A review of 78 cases from 14 published literature showed a good efficacy in improving asthma control. In most studies, aspirin tolerance was restored.⁴²

Allergic bronchopulmonary aspergillosis (ABPA)

ABPA is characterized by severe asthma, recurrent and transient pulmonary infiltrates, blood eosinophilia, central bronchiectasia, and elevated serum total and *Aspergillus fumigatus*-specific IgE levels and *A. fumigatus*-specific IgG levels. A small prospective study showed that patients with ABPA exhibited a significant reduction in asthma exacerbations, exhaled nitric oxide levels, and

expression of FcεRI on basophils after omalizumab treatment.⁴³ A recent systematic review of 102 cases from 30 published literature summarized beneficial effects of omalizumab treatment against ABPA; significant improvement in ABPA symptoms, and reduction in frequency of exacerbations and steroid requirement to one tenth.⁴⁴

Asthma–COPD overlap (ACO)

Patients with ACO have lower quality of life and suffer from more complications than those with asthma or COPD alone. Both Maltby *et al.*⁴⁵ and Hanania *et al.*⁴⁶ reported that patients with ACO treated with omalizumab experienced improvements in asthma outcomes similar to those in patients without ACO.

Role of omalizumab in severe childhood allergic asthma

IgE in childhood asthma

Most childhood asthma is allergic asthma, and allergic inflammation of the respiratory tract results in airway hypersensitivity, a central feature of asthma. Improvement of airway hypersensitivity leads to improvement of most symptoms of asthma. In addition, airway hypersensitivity is low for a long period without acute exacerbations, especially before puberty, and suppression of symptoms is thought to lead to improvement of airway hypersensitivity.⁴⁷ In children, this leads to further improvement of clinical symptoms.⁴⁸ In other words, the symptom-suppressing effect of omalizumab is important in children.

Especially in children, there is an association between the clinical course of asthma and the serum IgE level. Therefore, reducing serum IgE is thought to be important in the treatment of childhood asthma.

Reports of omalizumab treatment in childhood asthma

General improvement and safety

Many reports show improvement of symptoms, acute exacerbations and reduction of emergency room (ER) visits by omalizumab treatment.^{49,50} Omalizumab treatment is likely to be effective in patients with a high FeNO level, high eosinophil count, and high periostin level, suggesting the presence of enhanced Th2-type immune response. However, it should be noted that the children included in this study were over 12 years old.³⁸

Forty-seven patients with severe allergic asthma aged 6–21 years (mean: 11.7 years) were included in the study on the safety of omalizumab. Compared with the previous year, asthma exacerbations were significantly reduced during omalizumab treatment [1.03 vs 0.8 after 12 months ($p < 0.001$)]. Hospital admissions were reduced by 96%. At 12 months, FEV₁ was improved and a corticosteroid-sparing effect was observed. No serious adverse events were reported during the follow-up period of 12 months.⁵¹

We investigated 38 Japanese children aged 7–16 years (mean: 10.7 years), with a median exposure to omalizumab of 116.6 weeks (range: 46.9–151.1 weeks). The most common adverse events were nasopharyngitis, influenza, upper respiratory tract infection, etc.⁵² All 38 patients used ICS throughout the 24-week study, and 14 patients could reduce ICS dose from baseline by average of 64.5 µg/day (13.2%), while only one patient had a dose increase (by 100 µg/day). As mentioned above, there are many reports that ICS dose could be reduced. Therefore, the efficacy and safety of omalizumab have been confirmed in children over 6 years old.

QOL

Improvement in QOL of asthmatic children and adolescents receiving omalizumab is correlated with improvement in QOL of

their caregivers and reduction in ICS use, but not with improvement of FEV₁.⁵³ As many studies reported the improvement of QOL, we also reported that continued use of omalizumab improved symptoms, daily activity, and nocturnal sleep score,⁵² especially physical and emotional scores, after 24 weeks of omalizumab use.^{52,54}

Viral-infection induced asthma

Use of omalizumab has been reported to reduce the frequency of acute exacerbation of asthma due to viral infection in autumn.⁵⁵ In children with allergic asthma, omalizumab treatment decreased the duration of rhinovirus (RV) infection, viral shedding, and the risk of RV illness. These findings provide direct evidence that blocking IgE decreases susceptibility to RV infection and illness.⁵⁶ This effect was observed even when omalizumab was introduced one month before the expected increase of acute exacerbations.⁵⁷

Laboratory tests

- i) Free IgE and total IgE: Free IgE decreased from an average of 150 ng/mL to less than 25 ng/mL during the first week of omalizumab administration and remained low while administration was continued. Serum total IgE level increased for several months after the start of administration, but gradually decreased with continued administration and decreased significantly over 2 years, from 3790 to 2128 ng/mL with 2-weekly administration and 1580 to 984 ng/mL with 4-weekly administration. Figure 4 shows the changes of ER visit and total IgE concentration.⁵²
- ii) Spirometry: For pulmonary function, many studies reported little obvious improvement, but a recent report showed that marked improvement was achieved by omalizumab administration for one year.⁵¹ It was reported that lung function improved over 12 months of omalizumab treatment, with FEV₁ increasing from 79% of the predicted value (pred) at baseline to 91% pred at 12 months. If the pretreatment lung function is relatively good, such as around 80% pred or more, improvement is rapid after starting omalizumab, but it takes time to improve in severe cases. When discussing this issue, lung function at the start of treatment should be considered.
- iii) FeNO: Use of omalizumab in children has been reported to reduce FeNO.⁵⁸ In our experience, if ICS is correctly inhaled, even for 3 days, FeNO may drop rapidly from 80 ppb to 20 ppb.⁵⁹ It should be noted that FeNO decreases with omalizumab, but FeNO decreases rapidly under the influence of ICS, and conversely may increase in some cases. In other words, the concomitant use of ICS must be considered when FeNO is employed as an index for efficacy of omalizumab.

Cost effectiveness

We examined the situation in Japan regarding cost effectiveness. Comparing the medical costs before and after use of omalizumab, medical costs were clearly reduced in patients who were hospitalized more than 8 times a year, but were the same or increased in patients with fewer hospitalizations.⁶⁰ However, can we consider the effectiveness of omalizumab in children only on the basis of health care costs? Children are in the developmental stage; if asthma is relieved, they can exercise, attend school, reduce the number of hospital visits, and improve academic ability, social functioning, psychological openness, etc. Both social and economic benefits can be expected in the future.

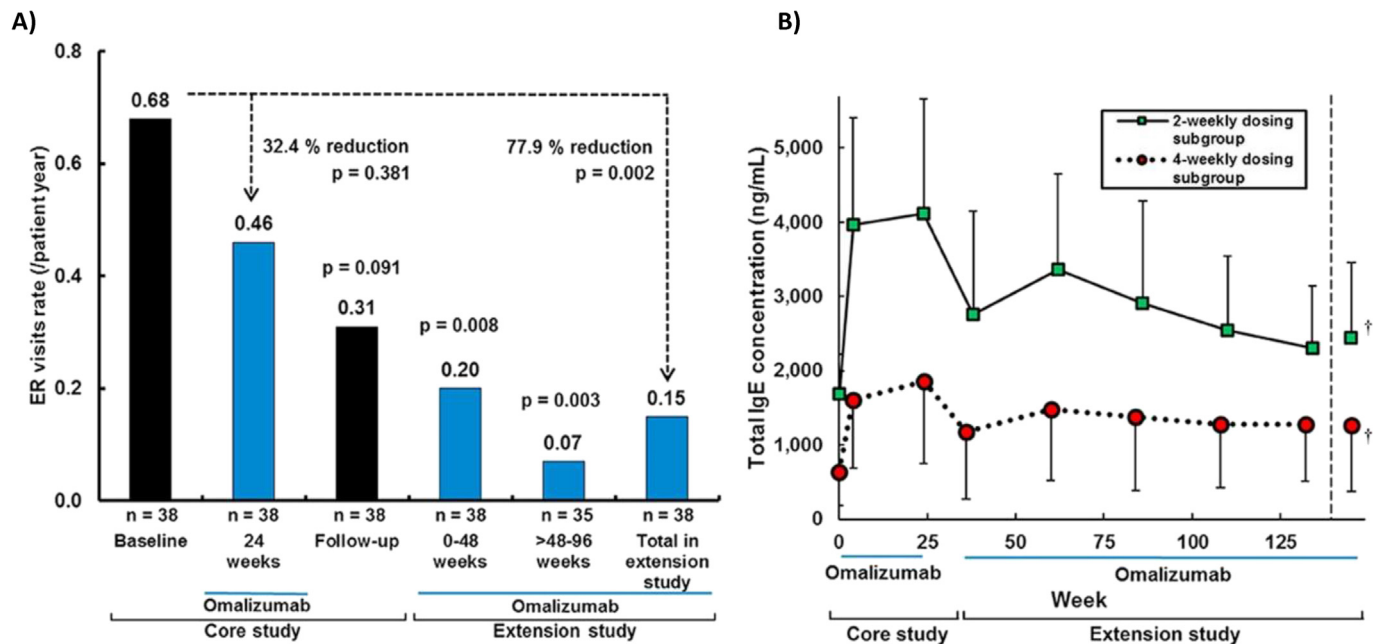


Fig. 4. Effects of omalizumab treatment on the rate of ER visits (A) and serum total IgE levels (B) in children with severe allergic asthma. (B) The serum total IgE level [mean (SD)] increased for several months after the start of administration, but gradually decreased with continued administration and decreased significantly over 2 years, from 3790 to 2128 ng/mL with 2-weekly administration (green square) and 1580 to 984 ng/mL with 4-weekly administration (red circle).⁵² † Values at the last visit of the extension study were summarized as the assessment of the end of the treatment period regardless of the patient's study duration.

Indications for omalizumab and future issues

As mentioned in the section on cost effectiveness, it is especially worth trying omalizumab in patients who are hospitalized frequently. However, the following points should be noted:

- (1) It is always necessary to check whether ICS are being inhaled properly.
- (2) Thorough examination of comorbidities and differential diagnoses (gastroesophageal reflux, aspiration, sinusitis, other respiratory disease, and atelectasis, etc.) is essential, and also check the environment (cigarette smoking, pets, etc.) before deciding the dose.
- (3) In our experience, it is difficult to obtain an effect in patients with a strong psychological component. However, it may be worthwhile if it is therapeutically useful for the patient to experience that asthma is improved by appropriate treatment.
- (4) When judging the effect based on changes of laboratory values such as lung function and FeNO, it is necessary to consider the severity and age at the start of treatment and the use of ICS. It is easy to improve asthma before puberty, but objective improvement is slower in severe cases. For omalizumab, improving symptoms is the first priority. Lastly, several issues listed in Table 1 should be solved in the future for the better use of omalizumab in the management of severe allergic childhood asthma.

Role of omalizumab in urticaria

Introduction and historical background

Urticaria is a commonly observed disease characterized by repeating emergence of transient and local edema of the skin or mucosa, mostly with itch. When symptoms repeat for 6 weeks or longer, they are classified as chronic urticaria (CU). CU is further

Table 1

Issues to be solved for the better use of omalizumab in severe allergic childhood asthma.

1. Can it be administered to seriously ill patients with high IgE levels? (Re-examination of serum IgE and dose). Can the dose be changed, such as when IgE falls during treatment?
2. What is the duration of continuous administration, timing of discontinuation, and treatment after discontinuation?
3. Can it be administered to children with asthma under 6 years old?
4. Consider the cost-effectiveness.
5. What should be done for severe asthma due to poor environmental factors?
6. Improvement of the formulation.
7. More appropriate administration method based on measuring free IgE.
8. Establish treatment for asthma associated with IgE-dependent allergic diseases (e.g., chronic urticaria and atopic dermatitis).
9. Examination of using other IgE-related treatments in combination for asthma (such as immunotherapy, immunosuppressants, and tolerance of food allergies).

classified into CSU and chronic inducible urticaria (CIndU).^{61–63} The identification and avoidance of trigger(s) are important for the management of CIndU, but not possible for CSU due to its characteristic, spontaneous appearance of wheals/angioedema without apparent triggers.⁶³ Up to 40% of CSU may be associated with autoantibodies against IgE or FcεRI (autoimmune-CSU). Among a variety of modalities for the treatment of urticaria, non-sedating 2nd generation antihistamine is the mainstay beyond the other medications. However, as many as 40% of patients with CSU remain in the non- or poorly controlled condition by antihistamines even at high doses.⁶² Since the approval of omalizumab for the treatment of CSU by EMA (EU) and FDA (USA) in 2014, and PMDA (Japan) in 2017, the application of omalizumab has been rapidly expanded in the treatment of urticaria.

The efficacy of omalizumab for urticaria was reported first by Boyce JA *et al.* in 2006⁶⁴ with a case of cold urticaria complicated with asthma, then by a study of 12 patients with autoimmune CSU,⁶⁵ followed by a study of non-autoimmune CSU.⁶⁶ Unlike for asthma, the fixed dose of 300 mg of omalizumab is optimal for CSU,

regardless of the patient's serum IgE levels and body weight.⁶⁷ The efficacy and safety of 300 mg omalizumab injections every 4 weeks on CSU were well proved by three pivotal studies,^{68–70} followed by meta-analysis and systemic reviews.^{71–73} No difference of its efficacy was found between autoimmune and non-autoimmune CSU.

Prognosis and parameters to predict efficacies of omalizumab

The initial effect of omalizumab on both disease severity and QOL of patients with CSU have been well documented by studies mentioned above.^{68–73} The analysis of 50 studies involving 921 patients showed that 89.5% patients were evaluated as having a complete or a partial response, and 10.5% as having no response or being refractory.⁷² A retrospective multicenter study with 470 patients with CSU in Italy revealed no difference in gender, age, disease duration and severity of urticaria between responders and non-responders to omalizumab.^{74,75} However, time course of response and relapse after the treatment with omalizumab may be different among patients. In most patients with CSU, clinically apparent improvement of the symptoms is observed within a week after the first injection,^{72,75} but may take longer duration in patients with autoimmune CSU⁷⁴ and/or low level of FcεRI expression on circulating basophils.^{76,77} Low levels of serum IgE,^{75,78,79} cell surface expression of FcεRI on circulating basophils,^{76,80–82} and eosinopenia⁸³ are reported to be associated with low- or no-responses to omalizumab (Table 2).

In spite of high efficacy under continuation of injections, urticaria may relapse in 4–8 weeks after the last injection of omalizumab.^{68–70} Although high level of serum IgE was associated with high and rapid effect of omalizumab, one study reported that the level of serum IgE higher than 100 IU/mL was reported to be associated with faster relapse of CSU.⁸⁴ On the other hand, two other studies contradict this result. One study suggests a significant relation of disease duration and severity (Urticaria Activity Score 7; UAS7),⁷⁵ but not the level of serum IgE with the time of relapse. The

other post-hoc study of 746 variables in the pivotal clinical studies^{68–70} revealed significant association of high baseline UAS7 and slow decrease of symptoms, represented by UAS7 scores across time points (UAS7 AAC) (Table 2).⁸² A study of resuming the treatment showed almost full recovery of control without developing neutralizing antibody.⁸⁵

The effect of omalizumab on CIndU and other skin diseases

A number of studies of omalizumab on CIndU have been reported.^{86,87} Although a body of evidences is small as compared with that for CSU, virtually all subtypes of CIndU have been proved to be reactive to omalizumab at the same or even lower doses as those for CSU. They include a double-blinded, placebo-controlled study on cold urticaria⁸⁸ and that on symptomatic demographism.⁸⁹

The effects of omalizumab on refractory atopic dermatitis have been reported mostly by several case reports and case series.^{90,91} Although the efficacy does not seem to be high as that for urticaria and remains controversial, it may be effective especially for children and patients with relatively low levels of serum total IgE without flaggrin mutation.^{90,91} A few trials with a combination with other modalities, such as intravenous immunoglobulin⁹² and immunoabsorption,⁹³ were reported to compensate a short of omalizumab to reduce high levels of IgE commonly observed in atopic dermatitis. A randomized, double-blinded, placebo-controlled study for the effect of omalizumab at dosing as that for asthma is ongoing for pediatric atopic dermatitis.^{94,95}

Several cases with other skin diseases treated with omalizumab, including urticarial vasculitis,⁹⁶ contact dermatitis,⁹⁷ and bullous pemphigoid⁹⁸ have also been published.

Mechanisms of actions of omalizumab in the pathogenesis of urticaria

The mechanism of action of omalizumab in the pathogenesis of urticaria is not fully clear. Omalizumab rapidly decreases level of circulating free IgE, followed by a decrease of IgE and FcεRI on basophils and mast cells in the skin.⁹⁹ It may explain the effect of omalizumab on the mediators release in response to IgG autoantibodies against IgE or FcεRI (type IIb autoimmunity). More recently, the presence of auto-IgE against various autoantigens such as thyroid peroxidase and IL-24 have been shown in sera of patients with CSU (type I autoimmunity) (Fig. 5). Omalizumab may also exert its efficacy by inhibiting the auto-IgEs which sensitize mast cells and induce histamine release from the mast cells in response to autoantigens.^{100,101} On the other hand, neither pre-incubation of basophils and skin mast cells nor pre-incubation of serum of CSU patients with omalizumab *in vitro* alters the histamine release from the cells in response to anti-IgE antibody or autoreactive CSU serum.¹⁰² We have demonstrated that basophils release histamine, when cell surface IgE was removed and re-

Table 2

Parameters to predict responses to and recurrence after stopping omalizumab in patients with CSU.

Parameters	Reference
<i>Poor response</i>	
Low serum IgE	72,75,77
Positive reaction in autologous serum skin test and/or basophil histamine release (activation) test	74,76
Low level of FcεRI on basophile	76,78,79
Low eosinophil number in peripheral blood (<50/mm ³)	83
<i>Rapid recurrence</i>	
High serum IgE (controversial)	75,84
High score of UAS7 before treatment	82
Long history of CSU before treatment	75
Small clinical improvement by initial treatment (UAS7 AAC)	82

CSU, chronic spontaneous urticaria; UAS7, Urticaria Activity Score 7; UAS7 AAC, Urticaria Activity Score 7 area above the curve.

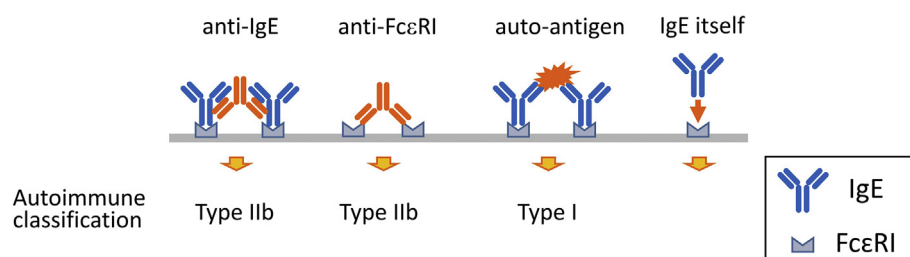


Fig. 5. Mechanisms of mast cell/basophils activation via IgE/FcεRI in urticaria.

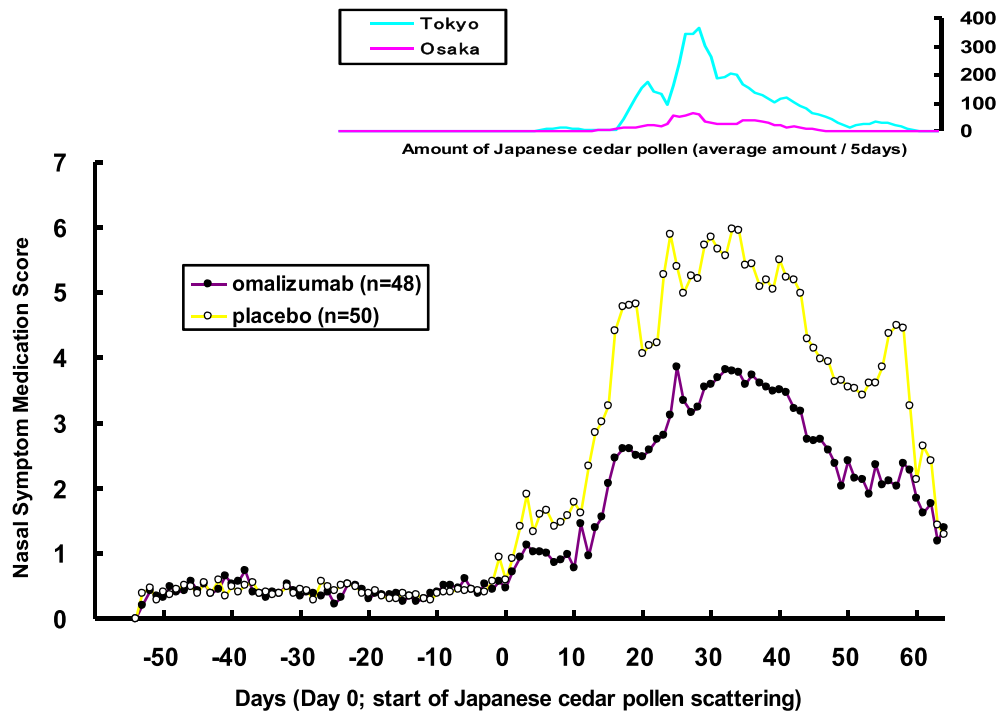


Fig. 6. Effects of omalizumab treatment on nasal symptom scores in patients with Japanese cedar pollinosis in 2002. The daily nasal symptom medication score was significantly reduced in omalizumab group (filled square) in Japanese cedar pollen dispersing season in Tokyo and Osaka compared to the score in placebo (open square).¹⁰⁹

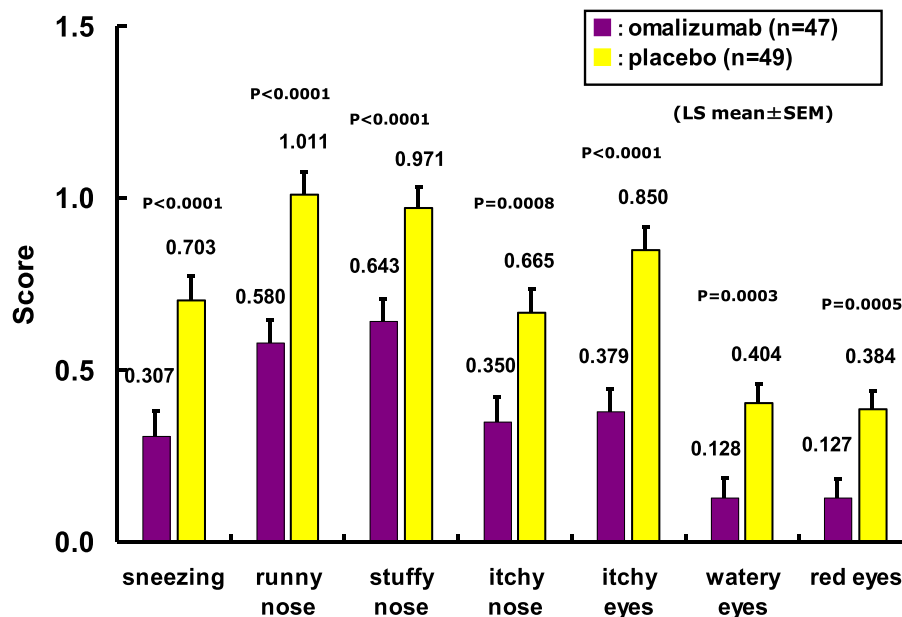


Fig. 7. Effects of omalizumab treatment on daily nasal and ocular symptom score in patients with Japanese cedar pollinosis in 2002. All symptoms score, sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes, were significantly reduced in omalizumab group (purple bar) compared with the score in placebo (yellow bar), especially in eye symptoms.¹⁰⁹

exposed to IgE. This reaction is enhanced by pretreatment of basophils with IL-3.¹⁰³ Since lifespan of basophils in the blood is only a few days,¹⁰⁴ it is feasible that newly developed basophils release histamine on the exposure to IgE in circulation, regardless of the presence of antigens and autoantibodies against IgE or FcεRI. Omalizumab should effectively inhibit this reaction. Another possible action of omalizumab is the inhibition of IgE binding to FcεRII on eosinophils. The successful treatments of refractory CSU

with antibodies targeting IL-5 and IL-5 receptor¹⁰⁵ support this possible action of omalizumab to eosinophils. On the other hand, ligelizumab, a newly developed humanized monoclonal anti-IgE antibody, specifically inhibits IgE-binding to FcεRI with higher affinity, and showed a higher efficacy on CSU than omalizumab in the recent clinical trial.¹⁰⁶ This result rather denies a crucial involvement of eosinophils in the mechanism of actions by omalizumab, since ligelizumab does not prevent IgE from binding to FcεRII.

Future perspectives

The application of omalizumab to urticaria has dramatically advanced the treatment of CSU and possibly other subtypes of CU, and shed light on its pathogenesis. Nevertheless, approximately 10% of the patients remains refractory, and a large part of the patients relapse after the cessation of omalizumab. The success of omalizumab in the treatment of urticaria prompted further development of various other medication which are in pipelines.¹⁰⁵ In parallel with the development of new medications, further understanding of the disease and better treatment of patients are expected.

Role of omalizumab for severe Japanese cedar pollinosis

Introduction

Treatment for allergic rhinitis including hay fever depends on suppressing some point in the flow of allergic reaction, from sensitization to a local immune reaction. Antigen-specific immunotherapy has its point of effect earlier than midway in the flow 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.

Effects of omalizumab against allergic rhinitis in the US and Europe

In the West, clinical trials of omalizumab treatment against allergic rhinitis have been conducted for several years by subcutaneous injection. Different from doses used in asthma, the trials for hay fever have been conducted at single doses of 150 mg or 300 mg of omalizumab. Casale *et al.* 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.¹⁰⁷ 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 doses of omalizumab 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 medications for emergency use was observed.¹⁰⁸

Effects on Japanese cedar pollinosis in Japan

In Japan, placebo-controlled comparative study and a comparative study with an anti-allergy drug were conducted on JC in 2002 and 2003, respectively. The placebo-controlled study used a dose concept of considering the level of omalizumab which can eliminate IgE systemically, in contrast to the overseas studies which had a set dosage of 300 mg. The amount of omalizumab was determined according to 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%, and significantly reduced ocular symptoms by 50% (Fig. 6). Individual symptoms of JC (itchy nose, sneezing, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes) were all significantly alleviated (Fig. 7). 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.¹⁰⁹

In 2003, a double dummy comparative controlled study with tosyl acid spulastat (IPD®), Th2 cytokine inhibitor, was conducted globally. 300 mg per day of IPD® was administered as initial treatment from beginning of February, and through the season. The nasal symptom medication score during the pollen dispersal season was 30% lower for omalizumab than IPD® (Fig. 8). 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.¹¹⁰

More recently add-on study of omalizumab for inadequately controlled severe pollinosis despite antihistamines and nasal corticosteroids has been conducted to determine the efficacy of add-on treatment with omalizumab in patients with inadequately controlled severe JC. In the 12-week, double-blinded, placebo-controlled, randomized study, severe JC patients whose symptoms were inadequately controlled despite nasal corticosteroids plus one or more oral medications in the previous two seasons were enrolled. The omalizumab group had significantly lower nasal and ocular symptom scores compared with placebo respectively, and these differences were clinically relevant. Omalizumab also improved quality-of-life scores as overall and in all domains versus placebo. No unexpected safety signals were observed. Based on these findings, omalizumab treatment for severe JC is now authorized, and is expected to be used from 2020 spring.

Conclusion

Omalizumab has introduced a paradigm shift in the management of severe allergic asthma and urticaria. The unique aspects of omalizumab, such as protective effects against viral infections and mast cell deactivation, should be emphasized. Since population suffering from pollinosis is large, there may be a concern on its economic impact of expanded use of omalizumab. However, when omalizumab is properly used under strict indications, patients with severe JC may greatly benefit from the treatment, which may lead to social benefits overall.

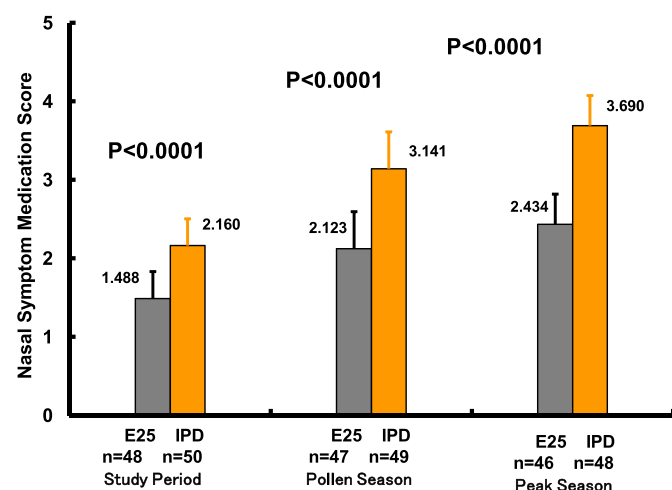


Fig. 8. The daily nasal symptom medication score in comparative study between omalizumab (E25) and IPD® for patients with Japanese cedar pollinosis in 2003. Nasal symptom medication score was evaluated in three periods such as study period, pollen dispersing period (pollen season), peak pollen dispersing 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).¹⁰⁹

Conflict of interest

HM, MH, and KO received honoraria from Novartis. HM received research funding from Novartis outside this review. The other authors have nothing to disclose.

References

- Wan T, Beavil RL, Fabiane SM, Beavil AJ, Sohi MK, Keown M, et al. The crystal structure of IgE Fc reveals an asymmetrically bent conformation. *Nat Immunol* 2002;**3**:681–6.
- Holdom MD, Davies AM, Nettlehip JE, Bagby SC, Dhaliwal B, Girardi E, et al. Conformational changes in IgE contribute to its uniquely slow dissociation rate from receptor FcεRI. *Nat Struct Mol Biol* 2011;**18**:571–6.
- Sutton BJ, Davies AM. Structure and dynamics of IgE-receptor interactions: FcεRI and CD23/FcεRII. *Immunol Rev* 2015;**268**:222–35.
- Sutton BJ, Davies AM, Bax HJ, Karagiannis SN. IgE antibodies: from structure to function and clinical translation. *Antibodies (Basel)* 2019;**8**:E19.
- Weskamp G, Ford JW, Sturgill J, Martin S, Docherty AJ, Swendeman S, et al. ADAM10 is a principal 'shedase' of the low-affinity immunoglobulin E receptor CD23. *Nat Immunol* 2006;**7**:1293–8.
- Lemieux GA, Blumenkron F, Yeung N, Zhou P, Williams J, Grammer AC, et al. The low affinity IgE receptor (CD23) is cleaved by the metalloproteinase ADAM10. *J Biol Chem* 2007;**282**:14836–44.
- Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008;**8**:205–17.
- van der Heijden FL, Joost van Neerven RJ, van Katwijk M, Bos JD, Kapsenberg ML. Serum-IgE-facilitated allergen presentation in atopic disease. *J Immunol* 1993;**150**:3643–50.
- Carlsson F, Hjelm F, Conrad DH, Heyman B. IgE enhances specific antibody and T-cell responses in mice overexpressing CD23. *Scand J Immunol* 2007;**66**:261–70.
- Aubry JP, Pochon S, Graber P, Jansen KU, Bonnefoy JY. CD21 is a ligand for CD23 and regulates IgE production. *Nature* 1992;**358**:505–7.
- Yu P, Kosco-Vilbois M, Richards M, Kohler G, Lamers MC. Negative feedback regulation of IgE synthesis by murine CD23. *Nature* 1994;**369**:753–6.
- Tu Y, Salim S, Bourgeois J, Di Leo V, Irvine EJ, Marshall JK, et al. CD23-mediated IgE transport across human intestinal epithelium: inhibition by blocking sites of translation or binding. *Gastroenterology* 2005;**129**:928–40.
- Palaniyandi S, Tomei E, Li Z, Conrad DH, Zhu X. CD23-dependent transcytosis of IgE and immune complex across the polarized human respiratory epithelial cells. *J Immunol* 2011;**186**:3484–96.
- Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;**164**:S6–11.
- Chen JB, Wu PC, Hung AF, Chu CY, Tsai TF, Yu HM, et al. Unique epitopes on CεMx in IgE-B cell receptors are potentially applicable for targeting IgE-committed B cells. *J Immunol* 2010;**184**:1748–56.
- Vigl B, Salhat N, Parth M, Pankevych H, Mairhofer A, Bartl S, et al. Quantitative *in vitro* and *in vivo* models to assess human IgE B cell receptor crosslinking by IgE and EMPD IgE targeting antibodies. *J Immunol Methods* 2017;**449**:28–36.
- Davies AM, Allan EG, Keeble AH, Delgado J, Cossins BP, Mitropoulou AN, et al. Allosteric mechanism of action of the therapeutic anti-IgE antibody omalizumab. *J Biol Chem* 2017;**292**:9975–87.
- Selb R, Eckl-Dorna J, Twaroch TE, Lupinek C, Teufelberger A, Hofer G, et al. Critical and direct involvement of the CD23 stalk region in IgE binding. *J Allergy Clin Immunol* 2017;**139**:281–9. e5.
- Eggel A, Baravalle G, Hobi G, Kim B, Buschor P, Forrer P, et al. Accelerated dissociation of IgE-FcεRI complexes by disruptive inhibitors actively desensitizes allergic effector cells. *J Allergy Clin Immunol* 2014;**133**:1709–19. e8.
- Foster B, Metcalfe DD, Prussin C. Human dendritic cell 1 and dendritic cell 2 subsets express FcεRI: correlation with serum IgE and allergic asthma. *J Allergy Clin Immunol* 2003;**112**:1132–8.
- Gill MA, Bajwa G, George TA, Dong CC, Dougherty II, Jiang N, et al. Counterregulation between the FcεRI pathway and antiviral responses in human plasmacytoid dendritic cells. *J Immunol* 2010;**184**:5999–6006.
- Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. *J Allergy Clin Immunol* 2012;**130**:489–95.
- Gill MA, Liu AH, Calatroni A, Krouse RZ, Shao B, Schiltz A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. *J Allergy Clin Immunol* 2018;**141**:1735–43. e9.
- Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;**108**:184–90.
- Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest* 2011;**139**:28–35.
- Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" Effectiveness studies of omalizumab in adult patients with severe allergic asthma: meta-analysis. *J Allergy Clin Immunol Pract* 2017;**5**:1362–70. e2.
- Ohta K, Miyamoto T, Amagasaki T, Yamamoto M. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. *Respirology* 2009;**14**:1156–65.
- Adachi M, Kozawa M, Yoshisue H, Lee Milligan K, Nagasaki M, Sasajima T, et al. Real-world safety and efficacy of omalizumab in patients with severe allergic asthma: a long-term post-marketing study in Japan. *Respir Med* 2018;**141**:56–63.
- Mauri P, Riccio AM, Rossi R, Di Silvestre D, Benazzi L, De Ferrari L, et al. Proteomics of bronchial biopsies: galectin-3 as a predictive biomarker of airway remodelling modulation in omalizumab-treated severe asthma patients. *Immunol Lett* 2014;**162**:2–10.
- Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration* 2011;**83**:520–8.
- Tajiri T, Niimi A, Matsumoto H, Ito I, Oguma T, Otsuka K, et al. Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study. *Ann Allergy Asthma Immunol* 2014;**113**:470–5. e2.
- Tajiri T, Matsumoto H, Gon Y, Ito R, Hashimoto S, Izuhara K, et al. Utility of serum periostin and free IgE levels in evaluating responsiveness to omalizumab in patients with severe asthma. *Allergy* 2016;**71**:1472–9.
- Slavin RG, Ferioli C, Tannenbaum SJ, Martin C, Blogg M, Lowe PJ. Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations. *J Allergy Clin Immunol* 2009;**123**:107–13. e3.
- Ito R, Gon Y, Nunomura S, Atsuta R, Harada N, Hattori T, et al. Development of assay for determining free IgE levels in serum from patients treated with omalizumab. *Allergol Int* 2014;**63**(Suppl 1):37–47.
- Gon Y, Ito R, Maruoka S, Mizumura K, Kozu Y, Hirayama H, et al. Long-term course of serum total and free IgE levels in severe asthma patients treated with omalizumab. *Allergol Int* 2018;**67**:283–5.
- Molimard M, Mala L, Bourdeix I, Le Gros V. Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control. *Respir Med* 2014;**108**:571–6.
- Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosen K, Chipps BE, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol* 2017;**140**:162–9. e2.
- Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;**187**:804–11.
- Matsumoto H. Treatment with anti-IgE monoclonal antibody and free IgE. In: Yokoyama A, editor. *Advances in Asthma: Pathophysiology, Diagnosis and Treatment*. Springer; 2019. p. 145–56.
- Casale TB, Chipps BE, Rosen K, Trzaskoma B, Haselkorn T, Omachi TA, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy* 2017;**73**:490–7.
- Hayashi H, Mitsui C, Nakatani E, Fukutomi Y, Kajiwara K, Watai K, et al. Omalizumab reduces cysteinyl leukotriene and 9α,11β-prostaglandin F₂ overproduction in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2015;**137**:1585–7. e4.
- Cameli P, Perruzza M, Salvini M, Fui A, Cekorja B, Refini RM, et al. Omalizumab treatment in Samter's triad: case series and review of the literature. *Eur Rev Med Pharmacol Sci* 2019;**23**:8124–9.
- Voskamp AL, Gillman A, Symons K, Sandrini A, Rolland JM, O'Hehir RE, et al. Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract* 2015;**3**:192–9.
- Li JX, Fan LC, Li MH, Cao WJ, Xu JF. Beneficial effects of Omalizumab therapy in allergic bronchopulmonary aspergillosis: a synthesis review of published literature. *Respir Med* 2017;**122**:33–42.
- Maltby S, Gibson PG, Powell H, McDonald VM. Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD. *Chest* 2017;**151**:78–89.
- Hanania NA, Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab effectiveness in asthma-COPD overlap: *Post hoc* analysis of PROSPERO. *J Allergy Clin Immunol* 2018;**143**:1629–33. e2.
- Odajima H, Baba M. [The relationship between respiratory threshold of acetylcholine and clinical course of asthma in children]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1989;**27**:456–60 (in Japanese).
- Odajima H, Baba M. [The relationship between reactivity and asthmatic attacks before and after acetylcholine inhalation test]. *Arerugi* 1992;**41**:1561–6 (in Japanese).
- McKeage K. Omalizumab: a review of its use in patients with severe persistent allergic asthma. *Drugs* 2013;**73**:1197–212.
- Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol* 2009;**124**:1210–6.
- Licari A, Castagnoli R, Denicolo C, Rossini L, Seminara M, Sacchi L, et al. Omalizumab in children with severe allergic asthma: the Italian real-life experience. *Curr Respir Med Rev* 2017;**13**:36–42.
- Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, et al. Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma. *Allergol Int* 2017;**66**:106–15.
- Sztafinska A, Jerzynska J, Stelmach W, Woicka-Kolejwa K, Stelmach I. Quality of life in asthmatic children and their caregivers after two-year treatment with omalizumab, a real-life study. *Postepy Dermatol Alergol* 2017;**34**:439–47.
- Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, et al. Omalizumab in Japanese children with severe allergic asthma uncontrolled with standard therapy. *Allergol Int* 2015;**64**:364–70.
- Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;**364**:1005–15.

56. Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med* 2017;**196**:985–92.
57. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes Jr SJ, Calatroni A, et al. Pre-seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;**136**:1476–85.
58. Silkoff PE, Romero FA, Gupta N, Townley RG, Milgrom H. Exhaled nitric oxide in children with asthma receiving Xolair (omalizumab), a monoclonal anti-immunoglobulin E antibody. *Pediatrics* 2004;**113**:e308–12.
59. Amimoto Y, Arakaki Y, Murakami Y, Masumoto N, Taba N, Tezuka J, et al. [Relationship between compliance with inhaled corticosteroids and changes in the fraction of exhaled nitric oxide during summer camp for asthmatic children]. *Arerugi* 2011;**60**:1641–5 (in Japanese).
60. Yoshikawa H, Iwata M, Matsuzaki H, Ono R, Murakami Y, Taba N, et al. Impact of omalizumab on medical cost of childhood asthma in Japan. *Pediatr Int* 2016;**58**:425–8.
61. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;**73**:1393–414.
62. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy* 2011;**66**:317–30.
63. Hide M, Hiragun T. Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries. *Allergol Int* 2012;**61**:517–27.
64. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol* 2006;**117**:145–8.
65. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008;**122**:569–73.
66. Ferrer M, Gamboa P, Sanz ML, Goikoetxea MJ, Cabrera-Freitag P, Javaloyes G, et al. Omalizumab is effective in nonautoimmune urticaria. *J Allergy Clin Immunol* 2011;**127**:1300–2.
67. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011;**128**:567–73. e1.
68. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013;**132**:101–9.
69. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015;**135**:67–75.
70. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;**368**:924–35.
71. Zhao ZT, Ji CM, Yu WJ, Meng L, Hawro T, Wei JF, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2016;**137**:1742–50. e4.
72. Bernstein JA, Kavati A, Sharp MD, Ortiz B, MacDonald K, Denhaerynck K, et al. Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: a systematic review of 'real-world' evidence. *Expert Opin Biol Ther* 2018;**18**:425–48.
73. Sharp MD, Bernstein JA, Kavati A, Ortiz B, MacDonald K, Denhaerynck K, et al. Benefits and harms of omalizumab treatment in adolescent and adult patients with chronic idiopathic (spontaneous) urticaria: a meta-analysis of "real-world" evidence. *JAMA Dermatol* 2019;**155**:29–38.
74. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;**139**:1059–61. e1.
75. Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. *J Eur Acad Dermatol Venereol* 2019;**33**:918–24.
76. Deza G, Bertolin-Colilla M, Sanchez S, Soto D, Pujol RM, Gimeno R, et al. Basophil FcεRI expression is linked to time to omalizumab response in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2018;**141**:2313–6. e1.
77. Asero R, Ferrucci S, Casazza G, Marzano AV, Cugno M. Total IgE and atopic status in patients with severe chronic spontaneous urticaria unresponsive to omalizumab treatment. *Allergy* 2019;**74**:1561–3.
78. Ertaş R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy* 2018;**73**:705–12.
79. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, et al. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. *Allergy* 2018;**73**:2406–8.
80. Deza G, Bertolin-Colilla M, Pujol RM, Cunto-Barredo L, Soto D, Garcia M, et al. Basophil FcεRI expression in chronic spontaneous urticaria: a potential immunological predictor of response to omalizumab therapy. *Acta Derm Venereol* 2017;**97**:698–704.
81. Deza G, March-Rodriguez A, Sanchez S, Ribas-Llaurado C, Soto D, Pujol RM, et al. Relevance of the basophil high-affinity IgE receptor in chronic urticaria: clinical experience from a tertiary care institution. *J Allergy Clin Immunol Pract* 2019;**7**:1619–26. e1.
82. Ferrer M, Gimenez-Arnau A, Saldana D, Janssens N, Balp MM, Khalil S, et al. Predicting chronic spontaneous urticaria symptom return after omalizumab treatment discontinuation: exploratory analysis. *J Allergy Clin Immunol Pract* 2018;**6**:1191–7. e5.
83. Kolkhir P, Church MK, Altrichter S, Skov PS, Hawro T, Frischbutter S, et al. Eosinopenia, in chronic spontaneous urticaria, is associated with high disease activity, autoimmunity, and poor response to treatment. *J Allergy Clin Immunol Pract* 2020;**8**:318–25. e5.
84. Ertaş R, Ozyurt K, Ozlu E, Ulas Y, Avci A, Atasoy M, et al. Increased IgE levels are linked to faster relapse in patients with omalizumab-discontinued chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;**140**:1749–51.
85. Maurer M, Kaplan A, Rosen K, Holden M, Iqbal A, Trzaskoma BL, et al. The XTEND-CIU study: long-term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2018;**141**:1138–9. e7.
86. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, et al. Omalizumab treatment in patients with chronic inducible urticaria: a systematic review of published evidence. *J Allergy Clin Immunol* 2018;**141**:638–49.
87. Di Leo E, Calogiuri G, Macchia L, Nettis E. Use of omalizumab in uncontrolled chronic spontaneous urticaria also improved latex-induced contact urticaria. *J Allergy Clin Immunol Pract* 2019;**7**:300–2.
88. Metz M, Schutz A, Weller K, Gorczyca M, Zimmer S, Staubach P, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol* 2017;**140**:864–7. e5.
89. Maurer M, Schutz A, Weller K, Schoepke N, Peveling-Oberhag A, Staubach P, et al. Omalizumab is effective in symptomatic demographism-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol* 2017;**140**:870–3. e5.
90. Wang HH, Li YC, Huang YC. Efficacy of omalizumab in patients with atopic dermatitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2016;**138**:1719–22. e1.
91. El-Qutob D. Off-label uses of omalizumab. *Clin Rev Allergy Immunol* 2016;**50**:84–96.
92. Toledo F, Silvestre JF, Munoz C. Combined therapy with low-dose omalizumab and intravenous immunoglobulin for severe atopic dermatitis. Report of four cases. *J Eur Acad Dermatol Venereol* 2012;**26**:1325–7.
93. Zink A, Gensbaur A, Zirbs M, Seifert F, Suarez IL, Mourantchian V, et al. Targeting IgE in severe atopic dermatitis with a combination of immunoadsorption and omalizumab. *Acta Derm Venereol* 2016;**96**:72–6.
94. Chan S, Cornelius V, Chen T, Radulovic S, Wan M, Jahan R, et al. Atopic Dermatitis Anti-IgE Paediatric Trial (ADAPT): the role of anti-IgE in severe paediatric eczema: study protocol for a randomised controlled trial. *Trials* 2017;**18**:136.
95. Chen T, Chan S, Lack G, Cro S, Cornelius VR. The role of anti-IgE (omalizumab/Xolair) in the management of severe recalcitrant paediatric atopic eczema (ADAPT): statistical analysis plan. *Trials* 2017;**18**:231.
96. Kolkhir P, Grakhova M, Bonnekoh H, Krause K, Maurer M. Treatment of urticarial vasculitis: a systematic review. *J Allergy Clin Immunol* 2019;**143**:458–66.
97. Mur Gimeno P, Martin Iglesias A, Lombardero Vega M, Bautista Martinez P, Ventural Lopez P. Occupational wheat contact dermatitis and treatment with omalizumab. *J Invest Allergol Clin Immunol* 2013;**23**:287–8.
98. Yu KK, Crew AB, Messingham KA, Fairley JA, Woodley DT. Omalizumab therapy for bullous pemphigoid. *J Am Acad Dermatol* 2014;**71**:468–74.
99. Metz M, Staubach P, Bauer A, Brehler R, Gericke J, Kangas M, et al. Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcεRI-positive cells in the skin. *Theranostics* 2017;**7**:1266–76.
100. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;**142**:876–82.
101. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase—a novel pathomechanism of chronic spontaneous urticaria? *PLoS One* 2011;**6**:e14794.
102. Gericke J, Ohanyan T, Church MK, Maurer M, Metz M. Omalizumab may not inhibit mast cell and basophil activation in vitro. *J Eur Acad Dermatol Venereol* 2015;**29**:1832–6.
103. Yanase Y, Matsuo Y, Kawaguchi T, Ishii K, Tanaka A, Iwamoto K, et al. Activation of human peripheral basophils in response to high IgE antibody concentrations without antigens. *Int J Mol Sci* 2018;**20**:45.
104. Kubo M. Mast cells and basophils in allergic inflammation. *Curr Opin Immunol* 2018;**54**:74–9.
105. Min TK, Saini SS. Emerging therapies in chronic spontaneous urticaria. *Allergy Asthma Immunol Res* 2019;**11**:470–81.
106. Maurer M, Gimenez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med* 2019;**381**:1321–32.
107. Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;**100**:110–21.
108. Adelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;**106**:253–9.
109. Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Allergol Int* 2006;**55**:379–86.
110. Nagakura T, Ogino S, Okubo K, Sato N, Takahashi M, Ishikawa T. Omalizumab is more effective than supalast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Clin Exp Allergy* 2008;**38**:329–37.