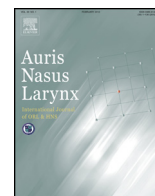




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Anti-IgE therapy to Kimura's disease: A pilot study

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ABSTRACT

Kimura's disease is a chronic disease that is characterized by subcutaneous granuloma of soft tissues in the head and neck region, increased eosinophil counts and high serum IgE levels. It is thought to be an IgE-mediated disease. Omalizumab, a monoclonal antibody, has recently been suggested as a potential new systemic treatment for IgE-mediated diseases, based on its efficacy in treating asthma and allergic rhinitis. We report a study of three patients with Kimura's disease who received anti-IgE (omalizumab) treatment. All patients were treated with a fixed schedule of eight cycles of omalizumab 300 mg, administered subcutaneously at intervals of 2 weeks. The size of tumorous regions was evaluated by MRI at base line and after 4 months of treatment. Blood samples were taken every month. In each of the patients, the size of tumorous regions and the peripheral blood eosinophil and basophil counts were all decreased after the treatment. These results suggest that omalizumab may be valuable for treatment of Kimura's disease.

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1. Introduction

Kimura's disease manifests primarily in the subcutaneous soft tissues and lymph nodes of the head and neck, but it can also develop elsewhere. Kimura's disease in the subcutaneous soft tissues leads to increased production of IgE antibodies and infiltration by eosinophils and mast cells, and it also causes the serum IgE level and the number of eosinophils in the blood to increase [1,2]. For those reasons, Kimura's disease is thought to be an IgE-mediated allergic disease. There is still no definitive treatment for this disease, although various therapies—including surgery—have been applied.

In recent years, an anti-IgE antibody, omalizumab, has been reported to show efficacy in treating asthma. Omalizumab binds to free IgE in the blood, thereby preventing IgE from binding to basophils and mast cells, inhibits activation of inflammatory cells and inhibits their release of such inflammatory mediators as histamine, leukotrienes, etc. [3]. It also inhibits Th2 cytokine release, suppresses eosinophils and down-regulates expression of Fc(epsilon)RI [3]. It is thought that omalizumab's suppression of IgE-mediated allergic reactions is due to these action mechanisms and its pharmacological activities.

Here, we report our findings regarding the efficacy of omalizumab in three Japanese patients with Kimura's disease that was not controlled by surgery.

2. Subjects and methods

Omalizumab was administered to three Japanese patients with Kimura's disease by injecting it subcutaneously at 300 mg/day in a total of 8 cycles given at two-week intervals. Blood examinations were performed for each patient before, during and after the treatment program. This study of treatment of Kimura's disease using this anti-IgE antibody (omalizumab) was approved by the Ethics Committee of Tokyo Women's Medical University (Approval No. 2547), and prior written informed consent was obtained from each of the patients.

2.1. Case 1

A 55-year-old male. Since about 15 years of age he had developed a mass extending from his right lower jaw to beneath his chin. At 30 years of age a doctor diagnosed it as Kimura's disease. He had undergone debulking of the mass three times. A mass beneath his chin was noted at the initial examination in our department. Steroid therapy (prednisone at 40 mg/day; tapering schedule) reduced the size of the mass, but it relapsed.

Omalizumab administration was started, and the mass beneath the chin began to shrink from the 2nd week. It had shrunk even more by 16 weeks after the start of the therapy (i.e., at the end of therapy) (Fig. 1A and B). MRI examinations also showed clear

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Fig. 1. Photographs of the neck region of each patient. Case 1 (A and B), Case 2 (C and D), Case 3 (E and F); A, C, and E: before treatment. B, D, and F: after 16 weeks of treatment (arrows indicate tumorous regions).

reduction in the size of the submental mass upon completion of the therapy compared with the pretreatment size (Fig. 2A and B). The patient showed no adverse reactions to omalizumab. The total IgE level in the serum initially increased after omalizumab therapy, but then decreased beginning from the 12th week after starting the treatment (Fig. 3A). The eosinophil and basophil counts in the blood had already decreased by the 4th week of treatment, and they remained low thereafter (Fig. 3B and C).

2.2. Case 2

A 49-year-old female. Beginning about the age of 46 years, she became aware of masses and itchiness in her left neck and behind her left ear. She was examined by a neighborhood physician and was directed to the authors' department for detailed examinations. Biopsy of cervical lymph nodes resulted in a diagnosis of Kimura's disease. Debulking of the mass was performed for the area behind her left ear, but the mass returned. Accordingly, anti-IgE antibody (omalizumab) therapy was started.

The mass below the left ear decreased in size beginning from the 2nd week of omalizumab therapy, and it was even smaller at the end of therapy (Fig. 1C and D). MRI confirmed that the mass in the left parotid gland had shrunk in size, and that the degree and number of swollen deep lymph nodes had both decreased (Fig. 2C and D). Skin itchiness was rated as VAS 8 before starting omalizumab therapy, and this decreased to VAS 4 at its completion. The total IgE level in the serum had decreased as of the 4th week of omalizumab treatment, but thereafter it gradually increased (Fig. 3A). The eosinophil and basophil counts in the blood gradually decreased after starting the omalizumab therapy (Fig. 3B and C).

2.3. Case 3

A 38-year-old male. A mass developed beneath his right ear beginning at about 28 years of age, and he visited the authors' department when he was 33. Kimura's disease was suspected on the basis of the palpation and MRI results, together with findings of elevated values for blood eosinophils and serum IgE. Tissue below the right ear was biopsied, and a diagnosis of Kimura's disease was reached. Debulking of the mass was performed, followed by steroid therapy (prednisone at 60 mg/day; tapering schedule). The mass recurred, and cytoreductive surgery was repeated. Steroid therapy was repeated, but the mass again relapsed. For that reason, anti-IgE antibody (omalizumab) therapy was administered.

Omalizumab administration was started, and the mass beneath the right ear gradually became soft beginning from the 8th week. By 16 weeks after the start of the therapy (i.e., at the end of therapy) the mass was smaller than initially (Fig. 1E and F). That reduction in size was confirmed by MRI (Fig. 2E and F). Skin itchiness was evaluated using a visual analog scale (VAS), and the score was 8 prior to the start of omalizumab therapy and decreased to 3 at its completion. The total IgE level in the serum increased until the 4th week of omalizumab treatment and thereafter remained almost constant (Fig. 3A). The eosinophil and basophil counts in the blood gradually decreased after the start of omalizumab therapy (Fig. 3B and C).

3. Discussion

Omalizumab is an anti-IgE monoclonal antibody that binds to free IgE in the blood, thereby decreasing the level of IgE antibodies in the blood. It also inhibits binding between IgE and FcεRI on the

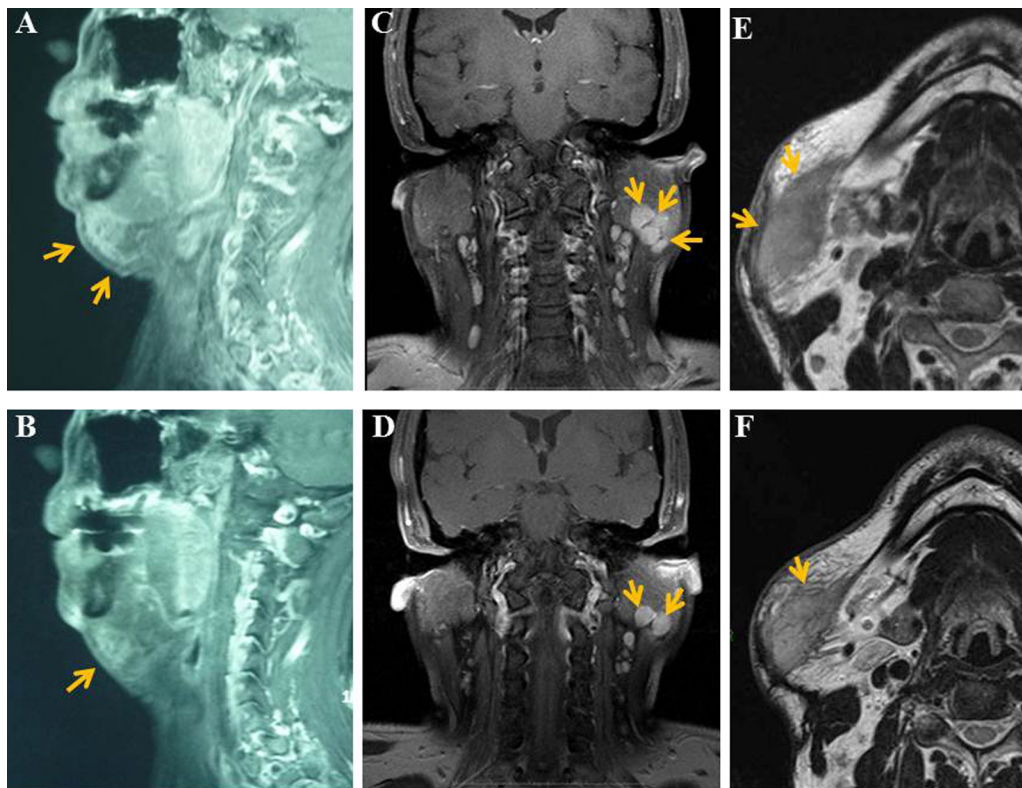


Fig. 2. MRI. Case 1 (sagittal section; gadolinium-enhanced, fat-suppressed T1-weighted image) (A and B); Case 2 (coronal section; gadolinium-enhanced, fat-suppressed T1-weighted image) (C and D); Case 3 (transverse section; T1-weighted image) (E and F); A, C, and E: before treatment. B, D, and F: after 16 weeks of treatment (arrows indicate tumorous regions).

surface of basophils and mast cells, as a result of which it inhibits the release of such inflammatory mediators as histamine, leukotrienes, etc., from those cells, and suppresses IgE-mediated allergic reactions [4]. Omalizumab is unable to bind to IgE molecules that are bound to FcεRI on cell membranes, and for that reason it is thought that there is basically no risk that it will cause anaphylaxis.

Omalizumab was investigated in the treatment of asthma in Phase III clinical trials conducted in the United States and Europe [5,6]. The drug was administered while reducing the dosage of inhaled steroid, and the frequency of exacerbation of symptoms, the frequency of use of β-agonists, improvement in respiratory function, etc., were investigated. Administration of omalizumab showed efficacy in reducing exacerbations and the steroid

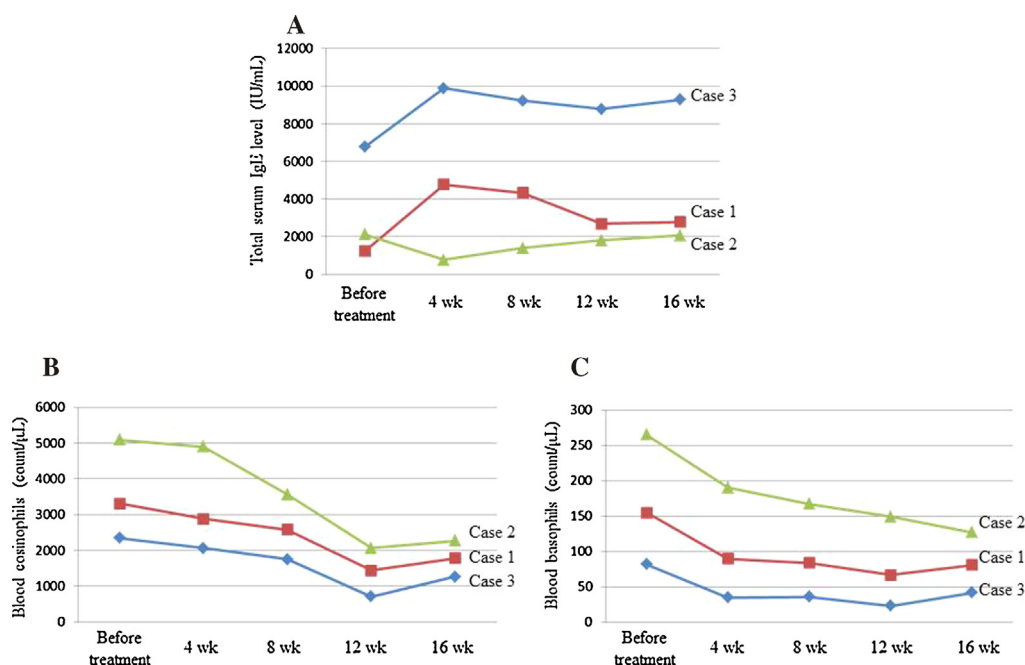


Fig. 3. Time-course changes in total serum IgE level (A), eosinophil count (B) and basophil count (C).

requirement [5,6]. In particular, it was reported that omalizumab was effective in severe asthma involving IgE because it significantly reduced the frequency of asthma exacerbations and reduced the dosage of steroid used [7]. In addition, omalizumab was reported to be effective in treating various asthma-associated conditions, i.e., allergic rhinitis, conjunctivitis, chronic sinusitis and eosinophilic otitis media [8–11]. Omalizumab was also found to be effective for such IgE-dependent allergic diseases as allergic bronchopulmonary aspergillosis and atopic dermatitis, even when they were not associated with asthma [12,13].

Omalizumab is a neutralizing antibody, and for that reason when it is used to treat asthma it is necessary that the serum total IgE level be in the range of 30–700 IU/ml. However, it was reported that omalizumab was effective even in patients with a serum total IgE level above 5000 IU/ml [14], and also that low-dose omalizumab was effective in atopic dermatitis patients with a high serum total IgE level [15]. Thus, omalizumab can be expected to be clinically effective even if the serum IgE is not completely neutralized by the antibody. It was surmised that this can be explained on the basis that omalizumab does not just neutralize serum IgE, but also lowers the IgE/IgG ratio [15]. In the three Kimura's disease patients we have reported here, as well, the baseline serum total IgE level was high at >1250 IU/ml, but omalizumab was clinically effective when administered in a dose of 300 mg.

Administration of omalizumab results in there being a mixture of free IgE and IgE–anti-IgE immune complexes in the blood. The half-life of IgE–anti-IgE immune complexes is approximately 14 days, which is longer than that of IgE. For that reason, it was reported that when omalizumab therapy is started, the serum total IgE level initially increases and does not decrease for a long time [16,17]. In our present three patients, as well, the serum total IgE level during omalizumab administration was the same or higher than the level prior to treatment.

There have been numerous reports that the blood eosinophil count decreases during omalizumab therapy, but the reason for that remains unclear. However, it might be because omalizumab administration inhibits the release of various mediators, including Th2 cytokines, from basophils and mast cells. In fact, Noga et al. [18] reported that omalizumab administration leads to apoptosis of eosinophils. It can be surmised that apoptosis is induced by the decrease in Th2 cytokines, which are important for differentiation and survival of eosinophils in the blood. It is interesting that Djukanović et al. [19] found that omalizumab administration to asthma patients reduced not just the blood eosinophil count but also eosinophils in sputum and the bronchial mucosa, while also reducing the numbers of IgE-positive cells, CD3-positive T cells, CD4-positive T cells, CD8-positive T cells, IL-4-positive cells and B cells in the bronchial mucosa. In our present three Kimura's disease patients, as well, the blood eosinophil count decreased starting from the 4th week of omalizumab therapy, and it can be surmised that the neck lesions shrank in size because the numbers of infiltrating inflammatory cells—such as eosinophils—decreased in response to the treatment.

Omalizumab was also reported to inhibit expression of FcεRI on basophils and suppress the release of histamine by basophils [20,21]. Earlier studies of allergic rhinitis found that the blood basophil count did not change in response to omalizumab administration [22,23]. However, in our three Kimura's disease patients, the blood basophil count decreased following omalizumab administration. These divergent findings might reflect differences in pathology between allergic airway diseases and Kimura's disease. Basophils, like mast cells, are target cells of anti-IgE antibody therapy, and the decrease in basophils seen in our three Kimura's disease patients might have an important meaning in regard to expression of the therapeutic effect of omalizumab.

Here, we have presented, for the first time, evidence of the efficacy of omalizumab therapy for Kimura's disease. To date, various therapeutic approaches have been taken for Kimura's disease, including drug therapy (steroids, anti-allergy drugs, non-steroidal anti-inflammatory drugs and antifungal agents) and surgical therapy (debulking). Unfortunately, however, there is still no definitive treatment for this disease. It is hoped that anti-IgE antibody therapy will be further developed for application to IgE-mediated allergic diseases. For Kimura's disease, as well, anti-IgE antibody therapy has the potential to be an important curative treatment.

Conflicts of interest

None.

References

- [1] Kimura T, Yoshimura S, Ishikawa E. On the unusual granulation combined with hyperplastic changes of lymphatic tissues. *Trans Soc Pathol Jpn* 1948;37:179–80.
- [2] Motoi M, Wahid S, Horie Y, Akagi T. Kimura's disease: clinical, historical and immunohistochemical studies. *Acta Med Okayama* 1992;46:449–55.
- [3] Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005;115:459–65.
- [4] Shields RL, Whether WR, Zioncheck K, O'Connell L, Fendly B, Presta LG, et al. Inhibition of allergic reactions with antibodies to IgE. *Int Arch Allergy Immunol* 1995;107:308–12.
- [5] 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.
- [6] Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254–61.
- [7] Holgate S, Bousquet J, Wenzel S, Fox H, Liu J, Castellsague J. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin* 2001;17:233–40.
- [8] Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;109:274–80.
- [9] Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004;59:1285–93.
- [10] Grundmann SA, Hemfort PB, Luger TA, Brehler R. Anti-IgE (omalizumab): a new therapeutic approach for chronic rhinosinusitis. *J Allergy Clin Immunol* 2008;121:257–8.
- [11] Okude A, Tagaya E, Kondo M, Nonaka M, Tamaoki J. A case of severe asthma with eosinophilic otitis media successfully treated with anti-IgE monoclonal antibody omalizumab. *Case Rep Pulmonol* 2012;2012:340525. <http://dx.doi.org/10.1155/2012/340525>.
- [12] Kanu A, Patel K. Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). *Pediatr Pulmonol* 2008;43:1249–51.
- [13] Thaiwat S, Sangasapaviliya A. Omalizumab treatment in severe adult atopic dermatitis. *Asian Pac J Allergy Immunol* 2011;29:357–60.
- [14] Kim DH, Park KY, Kim BJ, Kim MN, Mun SK. Anti-immunoglobulin E in the treatment of refractory atopic dermatitis. *Clin Exp Dermatol* 2012, October. <http://dx.doi.org/10.1111/j.1365-2230.2012.04438.x>.
- [15] Belloni B, Ziai M, Lim A, Lemerrier B, Sbornik M, Weidinger S, et al. Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. *J Allergy Clin Immunol* 2007;120:1223–5.
- [16] Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828–34.
- [17] Boulet LP, Chapman KR, Côté J, Kalra S, Bhagat R, Swystun VA, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997;155:1835–40.
- [18] Noga O, Hanf G, Brachmann I, Klucken AC, Kleine-Tebbe J, Rosseau S, et al. Effect of omalizumab treatment on peripheral eosinophil and T-lymphocyte function in patients with allergic asthma. *J Allergy Clin Immunol* 2006;117:1493–9.
- [19] Djukanović R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway

- inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170:583–93.
- [20] Eckman JA, Sterba PM, Kelly D, Alexander V, Liu MC, Bochner BS, et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol* 2010;125:889–95.
- [21] Noga O, Hanf G, Kunkel G, Kleine-Tebbe J. Basophil histamine release decreases during omalizumab therapy in allergic asthmatics. *Int Arch Allergy Immunol* 2008;146:66–70.
- [22] MacGlashan Jr DW, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;158:1438–45.
- [23] Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. *J Allergy Clin Immunol* 2004;113:297–302.