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CASE REPORT

Higher levels of soluble Fas ligand and transforming growth factor-β after omalizumab treatment: A case report

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A skewed T-helper (T_h)1/T_h2 immune response is considered to be the major cause of allergic disorders. Overproduction of T_h2 cytokines, which promote recruitment and activation of mast cells and eosinophils, plays a key part in the pathogenesis of allergic asthma. The mechanisms by which omalizumab is effective in asthma treatment are not yet fully understood. A 16-year-old girl who was experiencing frequent asthma attacks in spite of daily administration of budesonide (640 μg) and montelukast (10 mg) was given omalizumab (375 mg) at intervals of 2 weeks, to prevent a visit to the emergency room. Plasma levels of T_h1 cytokines [interferon (IFN)-γ and interleukin (IL)-12p70], T_h2 cytokines (IL-4 and IL-13), other proinflammatory and regulatory cytokines [IL-6, IL-10, IL-17, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β], chemokines [monocyte chemotactic protein (MCP)-1, chemokine ligand (CCL) 7, and CCL17], and soluble Fas ligand (sFasL) were measured before treatment and after treatment for 8 weeks. She showed a good clinical response to omalizumab: her lung function parameters improved and the use of β2-agonist decreased. No emergency room visits were required after omalizumab treatment for 8 weeks. Plasma levels of sFasL and TGF-β showed obvious increases after omalizumab therapy. IL-12p70 levels were decreased as compared to the corresponding baseline levels. These findings suggest that the effects of omalizumab in asthma treatment are not restricted to the regulation of the skewed T_h1/T_h2 cytokine immune

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response, and sFasL-mediated apoptosis and regulatory T-cell (Treg)-mediated TGF-β seem to have important roles in the therapeutic effects of omalizumab.

Introduction

Skewed T-helper (T_h)1/T_h2 immune response is the major factor responsible for allergic disorders. Overproduction of T_h2 cytokines, which promote recruitment and activation of mast cells and eosinophils, plays a key part in the pathogenesis of allergic disorders. Asthma is defined as a chronic airway inflammation mediated by T_h2 immune response and eosinophils. Inhaled corticosteroids (ICSs) are the major medication for asthma control. The other options for asthma control include leukotriene modifiers, theophylline, and long-acting β2-agonists.

Omalizumab, a recombinant monoclonal anti-immunoglobulin (Ig)E antibody (Ab), has proven efficacy in the treatment of allergic diseases. This drug is usually administered to patients with moderate-to-severe persistent allergic asthma that is inadequately controlled by treatment with medium- to high-dose ICSs and other controller medications. In addition to being used for the treatment of asthma, omalizumab is also effective for the treatment of allergic rhinitis and atopic dermatitis.[1] The mechanisms by which omalizumab is effective in asthma treatment are not yet fully understood.

We present here the case of 16-year-old girl in whom omalizumab treatment was administered because of frequent asthma acute attacks necessitating emergency room visits. Plasma levels of T_h1/T_h2/T_h3 cytokines, chemokine, and soluble Fas ligand (sFasL) were measured. On the basis of our observations, we suggest a new therapeutic mechanism for omalizumab.

Case report

A 16-year-old girl developed respiratory allergies to house dust mite and showed symptoms of seasonal rhinitis and asthma. Despite receiving treatment with high doses of inhaled corticosteroids (budesonide, 640 μg/day) in combination with long-acting β_2-agonist and leukotriene modifier (montelukast, 10 mg/day), the patient's asthma remained poorly controlled. Repeated episodes of severe asthma (more than five visits to the emergency department per month) necessitated discontinuation of the patient's school education. For the treatment of these repeated episodes, the patient received omalizumab 375 μg at intervals of 2 weeks. The patient's asthma symptom score and β_2-agonist use were documented daily in diaries, and spirometry was performed at each visit. The differential peripheral leukocyte count and T-cell subsets were measured (Table 1). Plasma levels of T_h1 cytokines (IFN-γ and IL-12p70), T_h2 cytokines (IL-4 and IL-13), other proinflammatory and regulatory cytokines (IL-6, IL-10, IL-17, TNF-α, and TGF-β), chemokines (MCP-1, CCL7, and CCL17), and sFasL were also measured every month (Table 2). After 3 months of omalizumab treatment, it was possible to reduce the patient's long-term treatment could to budesonide 320 μg/day. She showed clinical improvement, which was evident by the absence of emergency department visits for severe attacks and a decrease in rhinitis symptoms. The respiratory function parameters of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) also improved from 43.5% to 54.4% and from 36.8% to 41.5%, respectively, of the predicted values. After omalizumab treatment, the girl was able to resume school attendance. The omalizumab treatment was stopped because of problems with health insurance. However, we found that the levels of sFasL and TGF-β dramatically increased but those of IL-12p70 decreased. The changes in the levels of other cytokines and chemokines were not prominent.

Discussion

The inflammatory properties of asthma have been well studied. IgE activates a variety of inflammatory cells, including mast cells and basophils, through interactions with receptors (FcεRI and FcεRII). The activation of mast cells by IgE and the resulting mediator release is the first step in the allergic inflammatory cascade. Proinflammatory mediators (such as prostaglandin D2, leukotriene C4, TNF-α, and a variety of T_h2-type cytokines, chemokines, and growth factors) released from activated mast cells are responsible for the initial symptoms of asthma and stimulate dendritic cells and additional T_h2-related inflammatory reactions.[2,3] The central role of IgE in allergic inflammatory asthma provided the rationale for the development of omalizumab.[4,5]

Omalizumab can bind to the constant region of the IgE molecule, thereby preventing the interaction of IgE with IgE receptors on inflammatory cells and decreasing inflammatory cell activation. Omalizumab can decrease the

Table 1 Changes in leukocyte subpopulations and IgE due to omalizumab treatment

	Pre-Tx	1 month
WBC (/mm^3)	9700	8100
Eosinophils (/mm^3) (%)	281 (2.9%)	121 (1.5%)
CD3 (/mm^3) (%)	1605 (64%)	1186 (67%)
CD4 (/mm^3) (%)	818 (33%)	674 (38%)
CD8 (/mm^3) (%)	650 (26%)	435 (25%)
CD19 (/mm^3) (%)	444 (18%)	347 (20%)
Total IgE (KU/L)	599	1202

WBC: white blood cells; IgE: immunoglobulin E.

Table 2 Changes in cytokine and chemokine levels due to omalizumab treatment

	Pre-Tx	1 month	2 months
FasL (pg/ml)	58.5	6.56	103.5
T_h1 cytokines			
IL-12p70 (pg/ml)	3.51	0.06	0
IFN-γ (pg/ml)	13.72	13.08	13.39
IFN-α (pg/ml)	57.84	80.49	45.96
T_h2 cytokines			
IL-4 (pg/ml)	93.98	97.49	94.94
IL-13 (pg/ml)	10.68	10.98	11.4
Pro-inflammatory and other regulatory cytokines			
IL-6 (pg/ml)	0	0	0
IL-8 (pg/ml)	8.82	0	61.06
TNF-α (pg/ml)	14.81	15.14	12.90
TGF-β1 (pg/ml)	617.2	1752.8	14768
IL-17 (pg/ml)	10.18	9.43	9.54
Chemokines			
CCL17 (pg/ml)	19.63	5.75	17.54
MCP-1 (pg/ml)	322.27	340.19	163.3
MCP-3 (pg/ml)	32.35	34.11	32.79

FasL: Fas ligand; T_h: T helper; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; TGF: transforming growth factor; CCL: chemokine ligand; MCP: monocyte chemotactic protein.

circulating levels of unbound IgE but not those of total IgE.[6,7] Reductions in the circulating level of IgE leads to further reductions in FcεRI expression on mast cells, basophils, and dendritic cells.[6] Omalizumab can reduce the eosinophil count in sputum and bronchial biopsies[8,9] and can suppress T_h2 immune response by reducing the number of IL-2^+ and IL-13^+ T lymphocytes and the circulating IL-5 and IL-13 levels[4,10] without effecting the IFN-γ concentration. In our patient, the total serum IgE level was increased and the eosinophil count was decreased after omalizumab therapy. However, instead of the IL-4 or IL-13 levels, the plasma IL-12p70 levels were decreased after omalizumab treatment. In contrast, the TGF-β levels were increased after omalizumab treatment. Omalizumab may also suppress some T_h1 cytokines, presumably via the production of the Treg mediator TGF-β.

Moreover, omalizumab has been reported to show additional anti-inflammatory activity by inducing eosinophil apoptosis through an unknown mechanism.[9,11]

Further studies involving more patients cases and a longer treatment period are needed to confirm our observation. However, we found that the plasma sFasL level showed an obvious increase after omalizumab treatment. This might support a solution for the apoptosis and decrease of eosinophils.

In conclusion, our finding suggests that in addition to regulating the skewed balance of T_h1/T_h2 cytokines, omalizumab has other effects in asthma treatment. The apoptotic ligand sFasL and the Treg mediator TGF-β may also be important mediators for the therapeutic effects of omalizumab.

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