Severe persistent asthma responsive to off-label use of omalizumab despite high and low levels of total serum IgE

Asma persistente grave com resposta ao uso *off label* de omalizumabe, não obstante a IgE sérica total ser alta ou baixa

Nobuhiro Asai, Yoshihiro Ohkuni, Akina Komatsu, Ryo Matsunuma, Kei Nakashima, Norihiro Kaneko

Here, we present two cases of patients with severe persistent asthma. The two patients differed in terms of the total serum IgE level, which was quite high in one and quite low in the other. Despite the fact that the level of total serum IgE was not within the recommended range in either case, we opted to treat both with omalizumab. The treatment responses were favorable, and neither patient experienced any omalizumab-related side effects.

The first case (Case 1) was in a 75-year-old woman who visited our hospital for an asthma evaluation. Her asthma had been poorly controlled despite multi-drug therapy with salmeterol (100 µg/day), fluticasone (1,000 µg/day), ciclesonide (200 µg/day), tiotropium (18 µg/day), montelukast (10 mg/day), fexofenadine (60 mg/day), and theophylline (200 mg/day). As can be seen in Table 1, she had an asthma control test (ACT) score of 7 at the initial evaluation. The total serum IgE level was 1,149 IU/mL, and she tested positive for specific IgE to house dust and mites. In the previous year, she had had numerous asthma exacerbations, resulting in 7 emergency room visits and 6 hospitalizations. With the consent of the patient, we decided to initiate treatment with omalizumab, despite the fact that her total serum IgE level was well above the recommended cut-off value of 700. Omalizumab (300 mg/kg of body weight) was administered every two weeks for 16 weeks. The dose was determined to be identical to that which would be given based on the high IgE level. The patient reported an improvement in her quality of life immediately (after the first dose), and her ACT score rose to 25 (the maximum score). There were also improvements in PEF and FEV_1 (Table 2). We therefore classified the patient as an omalizumab responder, and the treatment was characterized as definitely effective. Thereafter, we maintained her on omalizumab (150 mg/kg every 4 weeks). While under treatment with omalizumab, she had no asthma exacerbations or emergency room visits and her quality of life remained satisfactory (Table 2).

The second case (Case 2) was in a 50-year-old woman who had been followed at an outpatient clinic since she was 20 years of age. She was also receiving multi-drug therapy, with salmeterol (100 µg/day), fluticasone (1,000 µg/day), montelukast (10 mg/day), and theophylline (400 mg/day). Nevertheless, her asthma was poorly controlled, and her ACT score at the initial evaluation was 13 (Table 1). Her total serum IgE level was quite low (20 IU/mL). She had twice been on mechanical ventilation because of severe asthma exacerbation and had received rescue medication (intravenous corticosteroids and aminophylline). During the previous year, she had visited an emergency room once every two weeks. She consented to off-label use of omalizumab, and we therefore administered the drug (150 mg/kg of body weight) every four weeks. The dose was determined to be identical to that which would be given based on the low total serum IgE level. After the initial dose of omalizumab, her ACT also rose to 25. Comparing the previous year with the 9-month follow-up period (Table 2), we found that the number of asthma exacerbations, emergency room visits, and hospitalizations decreased dramatically (from 3 to 0, from 22 to 1, and from 3 to 0, respectively). As in Case 1, we thereafter maintained her on omalizumab (150 mg/kg every 4 weeks). Her asthma remained under control, and the theophylline was therefore discontinued. There were post-treatment improvements in PEF and FEV_1 comparable to those observed in Case 1 (Table 2). This patient also responded well to treatment with omalizumab, despite her low total serum IgE level prior to treatment.

Clinical trials have demonstrated that omalizumab added to standard asthma therapy reduces exacerbations and emergency room

visits, with concomitant improvements in asthma control and quality of life, in patients with severe persistent asthma.[1] Add-on omalizumab is indicated for patients with a baseline total serum IgE level of 30-700 IU/mL and is administered every two or four weeks at a dose determined based on body weight and on the total serum IgE level prior to treatment.[2] In fact, there are many individuals with severe persistent asthma who, despite treatment with high doses of inhaled corticosteroids and β_2 agonists, have low or high levels of total serum IgE.

A sub-analysis of data from a large multicenter study demonstrated that omalizumab is less beneficial for patients with a total serum IgE level of 0-75 (IU/mL), even for those testing positive for perennial allergen-specific IgE.[3] Low total serum IgE levels might be caused by long-term treatment with oral corticosteroids or by local production of IgE in the lower respiratory tract only, such as that seen in non-atopic asthma.[4] Humbert et al. demonstrated that total IgE levels tend to decline with age in individuals with non-atopic asthma.[5] Some authors have questioned the existence of non-atopic asthma, suggesting that asthma always has an IgE-dependent component.[5-7] If tests for serum-specific IgE are negative, tests such as the skin prick test and the patch test, which are more sensitive than is serum-specific IgE testing, can be used.[8] Allergen-specific IgE rated as class 3-5 on the radioallergosorbent test (RAST) constitutes a causative factor for allergic reactions. In contrast, IgE with a RAST class of 1 and 2 are not always related to allergy. We believe that the RAST classification is not reliable enough to be the deciding factor in whether a given asthma patient should be treated with omalizumab. In addition, total serum IgE levels do not always reflect the severity or activity of asthma. Therefore, some severe persistent asthma patients with total serum IgE levels that lie outside the 30-700 IU/mL range might

Table 1 - Patient characteristics, laboratory test results, and allergy skin test findings.

Variable	Case 1	Case 2
Anthropometrics		
Height, cm	150.7	153.5
Weight, kg	62.0	45.6
Hematology		
White blood cells, cells/μL	12,600	9,200
Neutrophils, %	68.0	58.4
Lymphocytes, %	20.0	24.0
Eosinophils, %	8.0	13.1
Basophils, %	0.0	1.0
Red blood cells, cells/μL	405×10^4	519×10^4
Hemoglobin, g/dL	12.8	14.8
Hematocrit, %	38.5	44.2
Platelets, cells/μL	26.9×10^4	21.5×10^4
Total IgE, IU/mL	1,149	20
Allergen-specific IgE, RAST class		
Japanese cedar	0	3
Japanese cypress	0	0
Cat dander	0	1
Dog dander	0	0
House dust 1	3	2
House dust 2	3	3
Mites 1	3	2
Mites 2	3	3
Aspergillus sp.	0	1
Candida sp.	0	1

RAST: radioallergosorbent test.

Table 2 - Asthma control test scores and spirometric findings, before and after add-on treatment with omalizumab, together with a before-and-after comparison of the frequency of asthma-related events.

Variable	Case 1	Case 2
Asthma control test, score		
Pre-treatment	7	13
Post-treatment	25	23
PEF, L/min		
Pre-treatment	197.0	150.0
Post-treatment	317.4	220.0
FEV_1, L		
Pre-treatment	0.94	1.21
Post-treatment	1.23	1.54
FEV_1, %		
Pre-treatment	52.51	64.40
Post-treatment	57.74	82.80
Emergency room visits, n		
Previous year	9	22
During treatment	0	1
Severe attacks, n		
Previous year	7	3
During treatment	0	0
Intravenous betamethasone administrations, n		
Previous year	8	11
During treatment	0	0
Hospitalizations, n		
Previous year	7	3
During treatment	0	0

respond to treatment with omalizumab, as occurred in the two cases presented here.

Expanding medical costs constitutes one of the most difficult public health problems in every country. Although omalizumab is an expensive drug, cost-effectiveness analysis has shown it to be cost-effective in patients with severe persistent asthma.[2] In both of our cases, the patients improved dramatically and good control of asthma was achieved. The number of asthma exacerbations and hospitalizations was significantly reduced in Case 1 and Case 2. After receiving treatment with omalizumab, both patients scored much higher on the ACT. In addition, neither patient has since required oral corticosteroids for reducing asthma exacerbations during evaluations. Maintenance oral corticosteroid therapy is frequently prescribed in order to achieve control in patients with severe persistent asthma. However, regular oral corticosteroid use is associated with significant systemic side effects, including cataracts, hyperglycemia among individuals without diabetes, osteoporosis, acne, weight gain, sleep disorders, and mood disturbances.[9] Omalizumab can also reduce the need for rescue and maintenance oral corticosteroids, as has previously been demonstrated.[10]

In conclusion, omalizumab could be useful in patients with severe persistent asthma that remains uncontrolled despite multi-drug therapy, even when the total serum IgE level is higher or lower than the recommended range of 30-700 IU/mL and there is no specific IgE. Taking medical expenses and cost-effectiveness into consideration, the physician has to be the judge of whether a given patient is an omalizumab responder and should remain under treatment with this drug.

Nobuhiro Asai
Resident, Kameda Medical Center, Kamogawa, Japan

Yoshihiro Ohkuni
Chief, Kameda Medical Center, Kamogawa, Japan

Akina Komatsu
Resident, Kameda Medical Center, Kamogawa, Japan

Ryo Matsunuma
Resident, Kameda Medical Center, Kamogawa, Japan

Kei Nakashima
Resident, Kameda Medical Center, Kamogawa, Japan

Norihiro Kaneko
Chief, Kameda Medical Center, Kamogawa, Japan

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