First Experience with Omalizumab in a Child with Severe Persistent Asthma in Turkey: Case Report

Türkiye'de Ağır Astımlı Çocuk Olguda Omalizumab ile İlk Deneyim

Mustafa ARGA, MD,[a]
Arzu BAKIRTAŞ, MD,[a]
İpek TÜRKTAŞ, MD,[a]
M. Sadık DEMİRSOY, MD[a]

[a]Department of
Pediatric Allergy and Asthma,
Gazi University Faculty of Medicine,
Ankara

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Yazışma Adresi/*Correspondence:*
Mustafa ARGA, MD
Gazi University Faculty of Medicine,
Department of
Pediatric Allergy and Asthma,
Ankara,
TÜRKİYE/TURKEY
mustafarga@gmail.com

ABSTRACT Human monoclonal anti-IgE antibody (omalizumab) is recently recommended at the fifth step of international asthma guidelines for the treatment of patients older than 12 years of age who have severe persistent allergic asthma uncontrolled despite treatment with high-dose inhaled corticosteroid (>800 μgr/day) in combination with a long-acting β2-agonist and oral leukotriene receptor antagonist and have serum total Ig E between 30-700 IU/ml. We started omalizumab as add-on treatment to a severe persistent asthmatic case who had two severe asthma attacks in the last three-month period, one of which was complicated with pneumomediastinium. This is the first experience with omalizumab in a child with severe asthma reported from our country. The first seven-month of omalizumab treatment resulted in significant improvements in quality of life and pulmonary functions as well as reductions in inhaled corticosteroid dose and daily symptom scores.

Key Words: Asthma; child; omalizumab

ÖZET Son yıllarda, bir insan monoklonal anti IgE antikoru olan omalizumab, uluslararası tedavi kılavuzlarında beşinci basamakta yüksek doz inhaler kortikosteroid (>800 μgr/gün), inhaler uzun etkili β2 agonist ve oral lökotrien reseptör antagonist tedavisine rağmen astımı kontrol altına alınamayan ve serum total IgE düzeyi 30-700 IU/ml arasında olan, 12 yaşından büyük, ağır persistan allerjik astımlı hastalar için önerilmektedir. Kliniğimizde, ağır persistan astım tanısıyla izlenen ve son üç aylık dönemde biri pnomomediastinum ile komplike iki ağır astım atağı gelişen olgumuza omalizumab tedavisi başlandı. Olgumuz, ülkemizde çocukluk çağı astım popülasyonunda bildirilen ilk omalizumab uygulaması olup, tedavinin ilk yedi aylık dönemi değerlendirildiğinde tedavi öncesine göre günlük astım semptom skorunda azalma, hayat yaşam kalitesinde ve solunum fonksiyonlarında iyileşme ve koruyucu inhaler steroid dozunda anlamlı düzeyde azalma sağlandı.

Anahtar Kelimeler: Astım; çocuk; omalizumap

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Severe asthma continues to be a significant morbidity and mortality problem despite treatment according to international asthma guidelines.[1] Humanized monoclonal anti-IgE antibody (omalizumab) is recently recommended at the fifth step of international asthma guidelines for the treatment of patients older than 12 years of age who have severe persistent allergic asthma uncontrolled despite treatment with high-dose inhaled corticosteroid (>800 μgr/day) in combination with a long-acting β2-agonist and oral leukotriene receptor antagonist and have serum total Ig E between 30-700 IU/ml.[2,3] In this article, we present our clinical experience with omalizumab in the first Turkish child case with severe persistent allergic asthma.

CASE REPORT

A 13-year-old male patient with severe persistent allergic asthma for two years and allergic rhinitis has been followed in our department since he was two years old. Between the period of September 2007 and January 2008, his asthma was partially controlled even with high-dose inhaled corticosteroid (budenoside 1000 μgr/day) plus a long-acting β2-agonist (inhaled formoterol capsule 2 x 12 μgr/day) and oral leukotriene receptor antagonist (montelukast 1 x 5 mg/day p.o). Between January-March 2008 he applied to our emergency clinic twice with the complaints of sudden chest pain and dyspnea. In both admissions, his clinical exacerbations were judged as severe asthma attack one of which was complicated with pneumomediastinum requiring intensive care management. The patient was investigated for other pathologies that might mimic asthma symptoms such as immune deficiency, bronchiectasis, cystic fibrosis, gastroesophageal reflux, chronic sinusitis, other congenital or acquired airway and lung pathologies for differential diagnosis at the time of asthma diagnosis. Some of these investigations for gastroesaphageal reflux, chronic sinusitis, obstructive sleep apnea as co-morbid disorders were again consultated to related departments before he was diagnosed as severe persistant asthma. Additionally, the compliance of the patient as well as inhalation technique and allergen elimination measures were checked several times in this period. In this period, systemic steroid treatment at a dose of 1 mg/kg/day was administered intermittently for 28 days and his inhaled corticosteroid dose was augmented to 2000 μgr/day. In the following six weeks, clinical status of the patient was assessed according to daily symptom score, weekly quality of life and biweekly clinical examination. During this time the patient displayed low scores of quality of life and pulmonary function tests, high daily symptom score and was evaluated as having uncontrolled asthma.[4] Finally, the patient was deemed suitable for anti IgE treatment in line with international asthma guidelines. He had already been sensitized to grass pollen and cat epithelium, determined by skin prick test when he was 2 years old. In addition to these aeroallergens, he developed sensitization to house dust mite (*Dermatophagoides pteronyssinus, cat epithelium, grass pollen mix, cereals pollen mix, Lolium perenne, Dactylis glomerata, Festuca rubra, Poa pratensis, Phleum pratense, Avena sativa, Hordeum vulgare, Artemisia vulgaris*) at 13 years of age. His total serum IgE level was 203 IU/L. According to recommended treatment protocol, he had been given monthly 300 mg/dose omalizumab subcutaneously according to his body weight and serum total IgE level since May 2008.

Clinical response of the patient to omalizumab treatment was assessed according to daily symptom score, weekly quality of life scale, biweekly clinical examinations and pulmonary function tests. At the fourth month of treatment, the patient was evaluated as having controlled asthma at biweekly visits owing to apparent improvement in asthma symptom load (Figure 1), quality of life (Figure 2) and pulmonary functions (Figure 3). Eventually he was judged as responsive to omalizumab treatment and the treatment was continued.

After the first 4-month period, the percentage of inhaled corticosteroid dose was tapered by %25

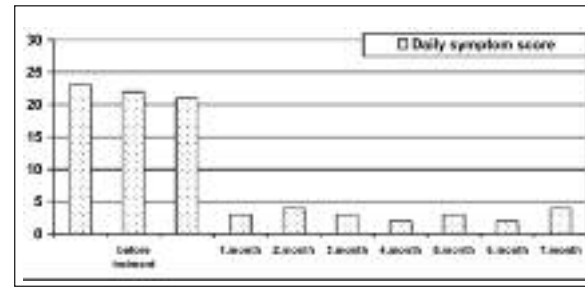

FIGURE 1: Mean daily symptom scores of the case before and after omalizumab treatment.

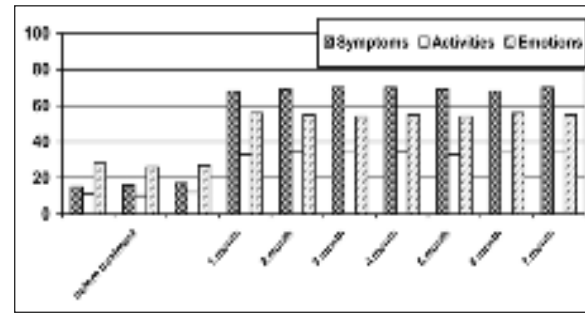

FIGURE 2: Quality of life scales of the case before and after omalizumab treatment.

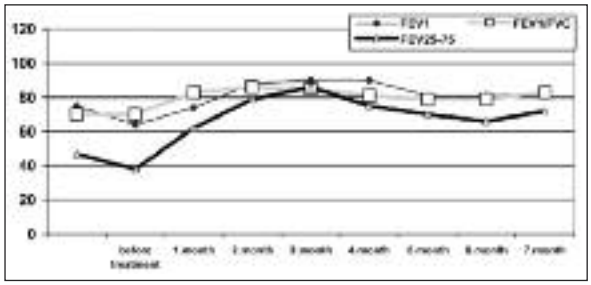

FIGURE 3: Pulmonary functions of the case before and after omalizumab treatment.

every six weeks. There was no deterioration in pulmonary functions, daily asthma symptom load or quality of life during step down. Our patient is now in the seventh month of omalizumab treatment receiving 1000 mg/day inhaled corticosteroid (budesonide), long acting β_2 agonist (formoterole inhaled capsule 2 x 12 μgr/day) and leukotriene receptor antagonist (montelukast 1 x 5 mg/day p.o).

No side effect was observed during omalizumab treatment. All administrations were applied ambulatory in our clinic by a trained nurse under the control of a doctor.

Informed signed consent was taken both from the parent and the patient.

DISCUSSION

This is the first experience with omalizumab in a child with severe asthma reported from our country. The first seven months of omalizumab treatment resulted in significant improvements in quality of life and pulmonary functions as well as reductions in inhaled corticosteroid dose and daily symptom scores.

Two thirds of patients with childhood asthma have an allergic origin which is more frequent in patients with severe persistent form.[5,6] Omalizumab is a human monoclonal antibody that binds free IgE in the circulation and prevents its attachment to both low and high-affinity receptors on the surface of mast cells and basophils, thereby preventing them from responding to allergens. This indirectly leads to decrement in allergic inflammation in the bronchi which ultimately provides improvement in asthma exacerbations and symptoms.[7]

There are seven randomized studies comparing omalizumab treatment with placebo in adolescents (≥12 y.o age) and adult patients.[8-14] Improvement in quality of life and reduction in emergency department visits and hospitalization rates were the common results of these studies when compared with the control groups.[15] Furthermore, in two of these seven studies inhaled corticosteroid doses could be reduced significantly.[10,12] Most of the studies published about omalizumab included both adults and adolescents except one which included 334 children aged 6 to 12 years with moderate-severe persistent asthma.[16] In this study, omalizumab group showed a remarkable ability to reduce (100% vs 66.7%, p= 0.001) and withdraw (55% vs 39%, p= 0.004) inhaled corticosteroid dose when compared to control group. The frequency of acute exacerbations was also significantly smaller in the omalizumab group (0.42 vs 2.72, p< 0.001). Likewise, in our case inhaled corticosteroid dose could be reduced to 50% at the seventh month of omalizumab treatment when his asthma was definitely controlled without any exacerbations. Moreover, the quality of life of our patient showed a significant improvement. In six of seven studies with omalizumab, there was no constant recovery in pulmonary functions except one which displayed remarkable improvement in FEV_1 at 32nd, 36th, 40th and 44th weeks of treatment.[11] In our case, the improvement in FEF_{25-75} was more pronounced than FEV_1. Systemic anti-inflammatory treatment is the most effective treatment of small airway obstruction. Hence in our case more favorable outcome of omalizumab in FEF_{25-75} may be related to its systemic use.

Previous studies showed that omalizumab was well tolerated and its safety profile was good. Most frequently encountered side effects were reactions at the injection site and headache.[17] It may seldomly cause anaphylaxis because of its protein nature. Systemic reactions due to administration usually develop in the first two hours, however this period may prolong to 24 hours. For this reason, American Academy of Allergy Asthma and Immunology recommends a two-hour observation period after the first three injections and a 30-minute observation period after the others.[18] This period

may be prolonged by doctors according to risk evaluation of the patient. We kept our patient under observation for eight hours in the first four treatments and for four hours in the remaining three. We did not observe any systemic reactions but a few local side effects such as swelling and pain at the injection site.

The baseline total serum Ig E level must be between 30-700 IU/ml in asthmatic patients who fulfill the indications of omalizumab treatment. Baseline serum total Ig E level and body weight of the patient are needed to determine the dose and the interval of omalizumab treatment. Monitorization of serum total Ig E level during or at the end of omalizumab treatment is not recommended. Compliance to asthma treatment, environmental control measures and investigations for both the differential diagnosis and co-morbid disorders of asthma must be reviewed before deciding the patient is a good candidate for omalizumab treatment. Therefore, at present Turkish Ministry of Health authorized omalizumab treatment only by a decision of a committee consisting of three specialists, either two chest physicians and one allergist or immunologist.

Unfortunately, there is still no single objective clinical or laboratory marker that predicts response to omalizumab treatment. However the best predictor for a good outcome was suggested as a combination of clinical parameters including symptom score, clinical examination and pulmonary function test and quality of life scale determined by the physician.[19] Therefore, considering the high cost of omalizumab, decision about the selection of patients with appropriate indications both to initiate and to continue treatment after a trial of 16 weeks is very important and should be done only in reference hospitals.

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