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Research Article

Which Ashma Phenotype have Poor Response to Omalizumab Treatment?

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Abstract

Background and Objective: Related with Th2/Th1 mix pathogenical pathway in severe allergic asthma; low eosinophilic-notrophilic and obese phenotype can be seen as an overlaping. This situation may effect response to omalizumab (OMB) treatment. We aimed in the study to determine the patients characteristic features who have poor response to OMB treatment.

Patients and Methods: Retrospectively collected data included patient demographics, comorbidities, documented exacerbations, urgent visits and hospitalizations for pre- and post-OMB initiation; results of lung function test, Asthma Control Test (ACT), blood eosinophil levels, serum total IgE, smoking status and Body Mass Index (BMI) were also recorded. If global evaluation of treatment effectiveness (GETE) scale were evaluated as excellent or good, we judged it as responder, if evaluated as moderate, poor, or worsening we judged it as non responder.

Results: The recorded data include 36 patients (10 male/ 26 female, mean age: 48.55 ± 10.14 years). While FEV1 (pred %) and ACT were improved, number of asthma attacks, emergency visits and hospitalizations were significantly decreased. 69.4% of the patients were evaluated as responders on the other hand 30.6% were considered as non-responders. Comparing with this two groups in non-responders eosinophil levels were significantly lower (non-responders: 160 cells/ µl; responders: 270 cells/ µl) but BMI was significantly higher (non-responders: 34 kg/m^2; responders: 27.7kg/m^2).

Conclusion: Related with the minimal Th2 pathogenic pathway, patients with high BMI and low eosinophil levels may have poor response to OMB treatment. İn the feature new targeting agents or OMB can be started according to dominant phenotypic feature and so extra cost can be prevented in severe asthma.

Keywords: *Asthma; Body Mass Index (BMI); Eosinophil; Omalizumab*

Introduction

Omalizumab (OMB) is a monoclonal anti-immunoglobulin E antibody developed for the treatment of asthmatic patients with inadequately controlled severe persistent allergic asthma despite optimal controller therapy [1]. It binds Fc region of free IgE and prevents it from interacting with the high affinity (FcεRI) receptor on the surface of mast cells and basophils and the low affinity (FcεRII) receptors of the B lymphocytes. Than inflammatory mediators, which contribute to acute and chronic symptoms of asthma are activated and released [2]. Ig E mediated asthma, characterized by production of distinct cytokines including IL-4, IL-5, and IL-13 from Th2-type [3,4]. But severe asthma has different pathology is characterized by a mixed Th2/Th1 phenotype with a possible contribution from Th17. Tumour necrosis factor (TNF)-α, IFN-γ, IL-17 and IL-27 are elevated in severe asthma and this cytokines may induce the neutrophils rather than eosinophils [5,6]. The Severe Asthma Research Program (SARP) to identify 5 different clusters of asthma phenotypes based on lung function, age of onset, atopy, sex, symptoms, and medication use. Clusters 1, 2, and 4 were identified as having early-onset atopic asthma but differed based on severity. Clusters 3 and 5 consisted of nonatopic subjects who were predominately women with late onset disease and associated obesity [7]. Another adult asthma cohort analysis from the Leicester group indicated that an eosinophilic phenotype may be more common in later onset severe asthma and identified four clusters including a similar early-onset atopic-asthma, an obese non-eosinophilic asthma, an early-onset symptom predominant-asthma, and a later onset inflammation predominant asthma [8].

OMB as an add-on therapy reduced the number of asthma exacerbations, reduced the concomitant medication burden, improved symptom severity, and improved quality of life [9]. However, it is a fact that not all patients with severe allergic asthma and IgE levels within the limits of administration, will benefit from omalizumab. The best predictors of response to OMB, were higher levels of Fractional exhaled nitric oxide (FeNO), blood eosinophils and serum periostin [10].

When we keep in mind that severe asthma is characterized by a mixed Th2/Th1 phenotype releated with the Th1 features, severe allergic asthma can also include intense smoking history, low eosinophilic-notrophilic and obese phenotype as an overlaping and so this sitiuation may effect response to OMB treatment. We aimed in the study to determine the patients characteristic features who have poor response to OMB treatment retrospectively.

Material and Methods

Our study is a retrospective study. Data collected from patients with severe refractory allergic asthma initiated omalizumab treatment between January 2013 and March 2016 according to the Global Initative for Asthma (GINA) guidelines [11]. All of them were severe uncontrolled allergic asthma despite high-dose inhaled corticosteroids (ICS) and long-acting beta agonists, with optimal inhaler technique and adherence. Clinically important pulmonary disease other than asthma (active lung infection, Chronic obstructive pulmonary disease, bronchiectasis), other causes of elevated peripheral eosinophil counts (allergic bronchopulmonary aspergillosis/mycosis and Churg-Strauss syndrome) were excluded. Collected data included patient demographics, comorbidities, OMB dosing, systemic corticosteroids prescriptions, documented exacerbations (defined as an increase in symptoms requiring treatment with systemic corticosteroids), urgent or unscheduled visits to the emergency department and hospitalizations for the 12 months pre- and post-OMB initiation; lung function test results and the patient-reported outcomes from the Asthma Control Test (ACT) [12]. The levels of blood eosinophils, serum total IgE, smoking status and BMI were also recorded. The study was approved by the ethics committee of our hospital.

Response to Omalizumab

After at least 1 year of OMB treatments effectiveness was evaluated, according to the physician's global evaluation of treatment effectiveness (GETE), by taking into consideration the improvement of night, daily symptoms, lung function and peak expiratory flow rate (PEF) by ≥ 15%, reduced usage of rescue medication, reduction of exacerbations. Furthermore, patients presenting with fully controlled asthma or a significant improvement in asthma control at the end of the evaluation period were characterized as responders. Taking acount of all these if the GETE scale were evaluated as excellent or good, we judged it as responder on the other hand if evaluated as moderate, poor, or worsening we judged it as non responder [13,14].

Statistical Analysis

Results are expressed as mean ± standard deviation (SD) when distributed normally otherwise median and range were used. Variables, such as lung function tests, visits to the emergency department, hospitalizations, ACT and so on, were analyzed by calculating the mean difference between post-OMB and pre-OMB, its 95% CI, and applying a paired t-test. Comparisons between groups of responders and nonresponders to OMB were performed using chi-square tests for categorical data, as well as unpaired t-tests or Mann-Whitney U-tests for normally distributed or without normally distributed numerical data, respectively. The statistical analysis were performed using the SPSS program (SPSS Inc. IL, USA) and p values were two tailed analysed. p values of less than 0.05 were considered statistically significant.

Results

The recorded data include 36 patients; composed of 10 male and 26 female, who were treated with omalizumab. The mean age was 48.55 ± 10.14 years and median total IgE was 433 IU/ml. Most patients (52.8%) has never smoked, Among smoked patients median smoking history was 4 package-year, only 5% of patients were current smokers and total of 13.8% patients smoking history were more than 10 packet -years. Prior to OMB initiation, detected perenial allergens of the patients were mostly house dust (88%) others were mould (22%), cat feather (11%) and *Blattella germanica* (5.5%). The drug allergy history was seen in 25% of patients and 2 of the patients with drug allergy history had also nasal polip, rhinosinusitis; responsible drug form was non-steroidal anti-inflammatory drug (NSAID) and so this patients diagnosed as aspirin-exacerbated respiratory disease (AERD). This 2 patients were also desensitizated with aspirin and they are taking the drug 600 mg per day with omalizumab treatment. When we look at comorbidities most commonly were seen A. Rhinitis (61%), secondly gastroesophageal reflux (27%) and then minimal bronchiectasis (13.8%), only one patient had congestive heart failure (CHF), with 44 kg/m^2 BMI and 64 years old women who was died because of the cardiac problems in second year of omalizumab treatment. Baseline and demographic characteristics of patients were given in table 1.

Variables	Patients treated with omalizumab (n = 36)
Age; years; mean (± SD)	48.55 (10.14)
Sex; Male/Female	10/26
ACT; mean (± SD)	7.80 (2.45)
Patints with smoking history; n (%) Package- year; median (range) Patients history with > 10 package year; n (%)	17 (47.2) 4 (1 - 15.75) 5 (13.8)
Exacerbations; median (range)	3 (0.5 - 12)
Emergency visits ; median (range)	24 (9 - 48)
Hospitalizations; median (range)	1 (0-2)
Total IgE IU/ml; median (range)	433 (128 - 662)
A.rhinits; n (%)	22 (61.11%)
Drug allergy History; n (%)	9 (25%)

Table 1: *Demographic charactesristics of patients.*
ACT: Asthma Control Test; BMI: Body Mass İndex

When we evaluated pre and post omalizumab effectiveness as FEV1 pred % and ACT were improved, number of asthma attacks required systemic steroid treatment, emergency visits and hospitalizations were significantly decreased. Only FEV (lt) was not significantly changed (Table 2).

	Pre Omalizumab	Post Omalizumab	P value
FEV1 lt	1.79	1.92	0.16
FEV1 %	62.87	69.48	0.03*
ACT; mean:	7.9	17.9	0.00**
Exacerbations; mean	11.45	1	0.00**
Emergency visits; mean	40.94	7.32	0.00**
Hospitalizations; mean	1.61	0.42	0.00**

Table 2: *Evaluation of Omalizumab effectiveness.*
ACT: Asthma Control Test; FEV1: Force Expiratory Flow.
**Statistical significant p < 0.05*
***Statistical significant p < 0.01*

According to patients response to omalizumab, 25 (69.4%) of them were characterized as responders while 11 patients (30.6%) were considered as non-responders. There is not any statistical significant regarding age and sex between responder and nonresponder groups. The number of patients with smoking history, history of patients with more than 10 packet-years smoking and mean packet years in both responder and non responder group were lower and not compareble. Comparing with responders and non responders; while eosinophil levels were significantly lower (270 to 160 cells/ µl), BMI was higher (27.7 to 34 kg/m2) in nonresponders. Age of onset asthma was higher in non responder group but does not have statistical significant (29.1 to 25.6; p = 0.57). There was not any differences as FEV1 or FEV1 % pred values between the groups (Table 3).

Variable	All (N = 36)	Responders (N = 25)	Nonreponders (N = 11)	p value
Eosinophil[1] (cells/µl) Eosinophil (%)	220 (70-370) 3.02 (0.99-4.58)	270 (120 - 390) 3.31 (1.28-5.58)	160 (40-200) 1.75 (0.5-3.05)	0.03* 0.03*
FEV1[2] (lt) FEV1 (%pred)	1.74 ± 0.81 61.86 ±2 2.42	1,82 ± 0.82 62 ± 21.47	1.56 ± 0.82 61.54 ± 25.55	0.42 0.95
BMI[2] (kg/m^2)	29.85 ± 6.61	27.7 ± 5.78	34.09 ± 6.45	0.006*
Age of onset ashma[2]	26.60 ± 16.34	25.6 ± 14,83	29.10 ± 20.31	0.57

Table 3: *Differences between responders and non-responders.*
[1]Data are presented at as median (interquartile range) and Mann- Witney U was used for comparing groups
[2]Data are presented as mean ± SD and t test was used for comparing groups
** Statistical significant p < 0.05*

Discussion

In this study, we have shown that OMB treatment reduced the attacks, emergency visits and hospitalizations, also improved the ACT and FEV1 pred% in generally responder and non responder groups of severe uncontrolled asthma sensitived to perenial allergens. Most of the patients have excellent or good responce named responders (69.4%); others were moderate or poor responce named nonresponders (30.6%); exactly all of them responded to the therapy although with little changes, except one patient without response in whom we have stopped the treatment. 3 patients had mild side effect one is only fatigue others had muscle or joint pain. We found that nonresponder group have higher BMI and lower eosinophil counts but FEV1 pred%, FEV1 (lt) and age of onset asthma were not different between the groups. When we deal with smoking history there was not enough patient for comparing with; behinds mean package year number was very low and most of them were give up smoking.

The clinical efficacy of omalizumab in reducing the asthma exacerbation rate was described in many clinical trials and "real-life" studies [15-18]. It is also well documented in the long term (3 years and beyond) efectiveness of the therapy conducted in Turkey [19,20]. In an earlier (15 month) real-life omalizumab study by Baybek., *et al.* from Ankara showed that reductions of asthma attacks, emergency hospital admissions, and hospitalizations by 93, 95, and 86%, respectively, relative to baseline were reported as Turkish data [21]. These findings were consistent with our data that we found the reductions 91.2, 82.1 and 73.9% respectively. As seen our hospitalization reduction rate was little diffrent this may be due to the study include small number of patients, and there were more risks for hospitalization in İstanbul than Ankara regarding air polition, humid wedher and so might be increase of mite sensitivity. Consistent with the multicenter study in Turkey conducted with Yorgancıoğlu., *et al.* [19] ACT also improved by clinically significant amounts and it is noteworthy that overall the responder groups ACT moved out of the poorly controlled range. Improvements in lung function were also seen and the difference from baseline was statistically significant for measurement of FEV1 (%predicted); but not for FEV1 (lt). This effect has not been demonstrated consistently in previous RCTs, but a similar effects were seen in other observational studies accompanied improvement of FEV1 (lt) also [22,23].

In our study we found that 69.4% of patients responded to treatment with OMB, which is consisted with the studies reporting that approximately 68.3% and other 61% of patients were responders [14,24]. In a previous study (10) higher FeNO and higher levels of blood eosinophils were related to better response to treatment with OMB, in our study the factor of blood eosinophil levels were related to response too. In an abstract presented in American thorax Society (ATS) conference they compared continuous effect with attenuated effect of 24 patients treated with OMB for 5 years, contrast to our study high BMI was releated with continuous effect [25]; thats why we did not know because there was not full text related with poster presentation. To our best knowledge there was not any other study about BMI and OMB effectiveness. When we look at baseline FEV1 values how effect the response; some studies showed that lower FEV1 which indicates more severe asthma had the most pronounced benefit of treatment with OMB [14,24]; but in our study there were not differences as baseline FEV1 values between responder and nonresponders.

Conclusion

Clinical features of patients treated with OMB were heterogeneous because of immunopathogenic cause is related with Th2/Th1 mix type. We found that related with the minimal Th2 pathogenic pathway, patients with high BMI and low eosinophil levels have poor response to OMB treatment. In the feature new targeting agents or OMB can be started according to dominat fhenotypic feature and so extra cost can be prevented in severe asthma.

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