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Airway inflammation and eotaxin in exhaled breath condensate of patients with severe persistent allergic asthma during omalizumab therapy

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ABSTRACT

Purpose: The central role of IgE in allergic inflammation in asthma has provided a rationale for the development of omalizumab, the humanized monoclonal anti-IgE antibody. The aim of the study was to determine the effect of omalizumab treatment on changes in airway inflammatory process and eotaxin in exhaled breath condensate in patients with persistent severe allergic asthma.

Material and Methods: The study was performed on a group of 19 patients with severe persistent allergic asthma treated with conventional therapy (according to GINA 2006) and with or without omalizumab (9 vs 10 patients). Eotaxin in exhaled breath condensate, exhaled nitric oxide, blood eosinophil count and serum ECP were measured before and after 16 weeks of therapy.

Results: In the group treated with omalizumab, a statistically significant decrease in the concentrations of eotaxin in EBC, FENO, serum ECP, and blood eosinophil count after 16 weeks of treatment was observed. Statistically significant correlations were revealed between the decrease in eotaxin and the decrease in FENO, serum ECP and blood eosinophil count after omalizumab therapy.

Conclusions: Downregulation of eotaxin expression in the airways through limitation of eosinophilic inflammation could be essential in the beneficial effect of anti-IgE therapy with omalizumab in asthma patients.

Key words: omalizumab, asthma, eotaxin, airway inflammation, exhaled breath condensate

INTRODUCTION

Omalizumab is a monoclonal anti-immunoglobulin E antibody developed for the treatment of asthmatic patients with inadequately controlled moderate to severe persistent allergic asthma despite optimal controller therapy [1].

Eosinophils have a well characterized role in asthmatic airway inflammation. The presence of eosinophils in airways is the consequence of a multistep and multifractorial process. Interactions of eosinophils with endothelial cells through adhesion molecules, and local generation of chemotactic agents involved in cell migration into the inflamed airways, are recognized as important mechanisms in the pathophysiology of airway inflammation [2]. The key factors affecting the increase in eosinophil chemotaxis to the site of inflammation as well as the prolonging of their survival, are IL-3, IL-5, and GM-CSF [3]. These act together with selective chemokines of eosinophils, such as eotaxin, RANTES, or MCP-4 (monocyte chemotactic protein-4). The strongest and the most specific chemoattractant is eotaxin [4, 5].

Mast cells and basophils are key cells connected with omalizumab activity. Mast cells have been closely associated with the cumulating inflammatory cells (including eosinophils), mucosal inflammation, endothelial activation, and bronchial hyperresponsiveness, through the release of cytokines such as Th2 cytokines, including interleukins 4 and 5 (IL-4, IL-5) and tumor necrosis factor – α (TNF-α) [6].

The mechanisms underlying the clinical and anti-inflammatory efficacy of omalizumab are not fully understood. There is no data concerning the effect of anti-immunoglobulin E treatment on eotaxin expression in the asthmatic airways.

The aim of the study was to assess changes in eotaxin

Table 1. **Characteristics of studied patients.**

Characteristics	Dimension	Patients treated with omalizumab	Patients without omalizumab	Differences between groups of asthma patients
Number of patients		9	10	
Sex	F/M	1/8	3/7	
Age	Years	49.3±8.2	52.0±8.6	p=0.95
Duration of symptoms	Years	13.4±8.1	15.3±12.5	p=0.67
Baseline FEV_1	% predicted	49.2±10.8	51.4±8.8	p=0.63
Blood eosinophil count	cells/mm^3	294.4±283.8	170.3±72.8	p=0.14
Baseline F_{ENO}	ppB	59.4±46.8	41.0±26.6	p=0.30
Serum total IgE	kU/L	218±123	156±150	p=0.36
eotaxin (EBC)	pg/ml	19.37±3.98	17.28±2.83	p=0.33
ECP (serum)	mcg/l	25.6±18.4	16.6±6.1	p=0.16
ICS dose[x]	mg/day	1138±253	1125±317	p=0.86

Data are presented as medians (ranges)
FEV_1- forced expiratory volume in one second
F_{ENO} – exhaled nitric oxide
ECP – eosinophil cationic protein
[x]Inhaled corticosteroids (Fluticasone propionate equivalent)

concentrations in the exhaled breath condensate (EBC) of asthmatics with severe persistent allergic asthma during omalizumab therapy as well as to establish the possible correlation of these measurements with other parameters of airway inflammation.

MATERIAL AND METHODS

Patients

The study was conducted on a group of 19 patients with severe persistent allergic asthma.

All patients used inhaled short-acting β_2-agonists (as rescue medication), inhaled long-acting β_2-agonists, high-doses of inhaled steroids (without oral steroids), and leukotriene receptor antagonists. It was an open-label study. Randomization was not performed. Nine patients with severe persistent allergic asthma who met criteria to receive omalizumab therapy were assigned to omalizumab therapy. Subsequently, 10 patients with severe allergic persistent asthma who met criteria to receive omalizumab therapy were assigned to the group treated with conventional treatment - recommended by GINA 2006 [7], without omalizumab. The authors have taken efforts to make the two studied groups comparable regarding the severity and kind of asthma, spirometric indices, intensity of day and night symptoms, and the controlling treatment used, as well as the necessity for rescue medication and other parameters used in asthma control assessment. All the patients were atopic and sensitized to common inhaled allergens, as evaluated by skin prick tests; they had total serum IgE of at least 30 to no more than 700 IU/ml. All patients had been in a stable condition, free from acute exacerbations and respiratory tract infections for the previous two months. They were non-smokers and during the last year had not been passive smokers.

Patients were treated with omalizumab on the basis of the concentration of serum total IgE and patient body weight at baseline [8]. The study protocol was approved by the Ethics of Research Committee of the Medical University of Bialystok, agreement number: R-I-002/68/2007. Informed consent was obtained from every patient entered into the study.

Measurements

Studied parameters were measured before and after a 16 week treatment period.

The measurements of exhaled nitric oxide (F_{ENO}) were performed by the chemiluminescence technique using a Sievers 280i NO Analyzer (Boulder, Colorado, USA). The measurements were performed on-line at an expiratory flow of 50ml/s [9]. Spirometry was performed according to ATS standards using a MasterScreen Pneumo PC spirometer (Jaeger, Hoechberg, Germany) [10].

Exhaled breath condensate was collected by using a commercially available condenser (EcoScreen; Erich Jaeger GmbH, Hoechberg, Germany) according to current ATS/ERS guidelines [11]. The longest storage time of EBC samples did not exceed two months. The samples were not concentrated prior to measurement. Because the marker used to correct the difference in the degree of dilution has not yet been established, in our study we made no attempt to assess the dilution of ALF in EBC. The results were well repeatable {CV(%)= 4-7%}. We performed the preliminary study, in which we measured eotaxin in EBC immediately after collection and after 1, 2, and 3 months of storage at -80ºC, and did not observe important changes. The concentrations of eotaxin (R&D Systems, Wiesbaden-Nordenstadt, Germany) in EBC were determined using an enzyme-linked immunosorbent assay. The minimum detectable level was 5.0 pg/ml.

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