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Article · December 2016

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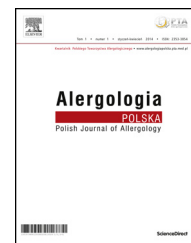
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Effectiveness of omalizumab therapy in patients with highly severe allergic asthma treated in Department of Pulmonology in Krakow

Skuteczność leczenia omalizumabem pacjentów z bardzo ciężką astmą alergiczną w Klinice Pulmonologii w Krakowie

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ARTICLE INFO

Article history:

Received: 23.10.2016

Accepted: 28.11.2016

Available online: 02.12.2016

Keywords:

- Asthma
- Omalizumab
- Therapeutic program
- Real-life study

Słowa kluczowe:

- astma
- omalizumab
- program terapeutyczny
- badanie w warunkach rzeczywistych

ABSTRACT

Immunoglobulin E plays an important role in allergic diseases. In patients with allergic asthma, exposure to allergens releases a wide range of proinflammatory mediators, which are responsible for acute and chronic symptoms of the disease. IgE has become an attractive target in allergic asthma. In 2006, in Europe omalizumab became available. **Objectives:** Our knowledge of who will derive the highest benefit from omalizumab therapy is still limited. The aim of this study was to evaluate the efficacy of omalizumab during one year of therapy carried out under real-life conditions in Polish patients with severe allergic asthma. We also attempted to identify predictors for very good responses to treatment. **Methods:** We enrolled 15 patients due to inclusion criteria of the program for severe allergic asthma funded by the National Health Insurance. All the patients were assessed for asthma control, quality of life, daily dose of oral and inhaled corticosteroids, asthma exacerbation rate, and lung function. The effectiveness of the treatment was analyzed after 16 weeks and one year following the inclusion each patient to the therapy. The patients were divided into two groups according to their response to the treatment: very good and good, based on the GETE scale. **Results:** Omalizumab decreased the severity of symptoms, improved asthma control and quality of life in patients. It helped to reduce episodes of asthma exacerbation and the use of systemic corticosteroids. At present, the overall assessment by physicians is still the best and most reliable method of identifying responders to the omalizumab therapy.

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<http://dx.doi.org/10.1016/j.alergo.2016.11.010>

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Introduction

Since its registration in the United States in 2003, and in Europe in 2006, omalizumab (OMA), the first biological medication employed in asthma treatment, has continued to arouse great interest. The drug has become another milestone in development of asthma therapy. Although in the majority of patients, asthma may be successfully controlled by inhaled corticosteroids (iGCS) with long acting β_2 -agonists (LABA) and anticholinergics, or possibly antileukotriene drugs (LTRA – leukotriene receptor antagonist) and/or theophylline, nevertheless, in approximately 5% of individuals, in spite of using the above pharmaceuticals in maximum doses, disease control fails to be achieved. Following the introduction of omalizumab, the drug was expected to become a remedy for patients with extremely severe allergic asthma. However, as it has turned out, the medication is highly effective, but not in each and every of the above patients. Omalizumab was introduced based on numerous clinical trials, in which it was employed in selected patients meeting the strict inclusion criteria. Thanks to such trials, and to proving that omalizumab was effective and safe, the medication was registered and became available to patients with asthma. However, in actual life, the population of patients that are on anti-IgE therapy is much more diversified. At present, there is emphasized the role of follow-up studies carried out in patients treated with omalizumab in daily practice, or the so-called “real-world” or “real-life” studies [1, 2]. Such investigations have been observed to allow for an ultimate verification the effectiveness of a drug in real life, already following its registration based on its efficacy determined in clinical trials [3]. This is of particular importance not only from the perspective of the patient that expects the drug to be effective, but also from the perspective of the insurer/payer that is responsible for public reimbursement of a given pharmaceutical that is interested in narrowing the group of patients to such individuals that will genuinely benefit from the drug usage. In case of omalizumab, studies continue to be carried out aiming at establishing in which patient this expensive therapy may culminate in the best effects. Biomarkers that might determine the above are searched for, so that the costs of treating asthma could be at least adequate to therapeutic effects. In Poland, similarly as in entire Europe, the drug was registered in 2006 and immediately introduced into therapy. However, in view of its cost, it was unavailable to many individuals. Already at that time, very good effects were noted in numerous patients. In 2013, the program of treating severe allergic asthma with omalizumab financed by the National Health Insurance was launched. The program envisioned inclusion of patients based on much more restrictive criteria than these defined in the summary of medicinal product characteristics (SmPC). SmPC allows for employing omalizumab in patients above six years of age, with documented severe allergic asthma with frequent diurnal and nocturnal symptoms and recurrent episodes of disease exacerbation in spite of administration of high daily doses of iGCS combined with LABA

[4]. Patients above 12 years of life should be also demonstrated to have deteriorated lung function ($FEV_1 < 80\%$ of the appropriate value). On the other hand, the program financed by the National Health Insurance may include patients above 12 years of life with severe, uncontrolled bronchial asthma (according to GINA (Global Initiative of Asthma)) who are allergic to perennial allergens what is confirmed by skin prick tests or determinations of specific IgE, in whom:

- It is necessary to use high doses of iGCS combined with LABA and possibly another asthma-controlling medication (anticholinergics and/or LTRA and/or a theophylline derivative).
- Within the past six months, oral GCS were (are still) employed due to poor asthma control.
- Total IgE is in the range of 30–1500 IU/ml.
- Body mass is within the range 20–150 kg.
- Additionally, meeting at least three of the below listed criteria is required:
 - Symptoms of uncontrolled asthma determined by means of ACQ (Asthma Control Questionnaire) above 1.5 points.
 - Three or more exacerbation episodes per year that require the use of systemic GCS or their dose in individuals on chronic GCS therapy.
 - Hospitalization due to asthma exacerbation within the past year.
 - A life-threatening incident of an asthma attack in the past.
 - Persistent respiratory obstruction ($FEV_1 < 60\%$ of the appropriate value or daily PEF changes $> 30\%$).
 - Deterioration of quality of life due to asthma determined by means of AQLQ (Asthma Quality of Life Questionnaire) below 5.0 points.

Objective

The objective of the present report is to describe the demographic and clinical profile of a patients receiving omalizumab treatment under the National Health Insurance drug prescription program and to evaluate the results achieved by the patients qualified for the above program and managed in the Department of Pulmonology in Krakow after 16 and 52 weeks of the therapy. The report is meant to be an input to the currently implemented “real life” investigation, i.e. follow-up studies carried out in patients treated with omalizumab in daily practice conditions.

Material and methods

The investigation was designed as an observational, prospective and single-center study. The patients were included into the study in keeping with the above presented inclusion criteria. They were diagnosed and managed according to the routine requirements of clinical practice and the program criteria described in the addendum to the Notice of Minister of Health, Appendix B.44 [5]. The patient assessment was performed after one year on omalizumab treatment.

Table I – Characteristics of the study group

	Combined groups	VGR response	GR response	p
Sex F/M % F	11/4 73.3%	8/0 100%	7/4 42.9%	p = 0.026
Sickness benefit/professionally active	Data not available	Data not available	Data not available	
Age at onset of treatment				
Mean ± SD	47.0 ± 10.6	49.3 ± 6.7	44.4 ± 14.0	p = 0.643
Median [25%–75%]	49.0 [42.0–54.0]	49.5 [44–55]	48.0 [26–52]	
Age at asthma diagnosis				
Mean ± SD	18.9 ± 15.1	22.9 ± 13.2	14.3 ± 16.8	p = 0.295
Median [25%–75%]	21.0 [16.0–37.0]	25.5 [12.5–33.0]	9.0 [1.0–33.0]	
Duration of asthma				
Mean ± SD	28.1 ± 12.8	26.4 ± 11.4	28.1 ± 12.8	p = 0.602
Median [25%–75%]	24.9 [3.0–33.0]	22.5 [18.0–35.5]	24.9 [3.0–33.0]	
Initial FEV1				
Mean ± SD	66.7 ± 21.5	66.3 ± 15.7	67.1 ± 28.1	p = 0.862
Median [25%–75%]	65.0 [49.0–79.0]	63.0 [53.5–78.5]	65.0 [39.0–91.0]	
ACQ				
Mean ± SD	3.01 ± 0.59	2.97 ± 0.59	3.05 ± 0.82	p = 0.487
Median [25%–75%]	3.00 [2.70–3.50]	2.93 [2.75–3.10]	3.20 [2.50–3.80]	
AQLQ				
Mean ± SD	3.45 ± 0.66	3.55 ± 0.55	3.34 ± 0.79	p = 0.452
Median [25%–75%]	3.47 [2.90–3.87]	3.49 [3.10–3.85]	3.10 [2.70–3.87]	
IgE				
Mean ± SD	266.2 ± 216.8	377.3 ± 224.7	139.3 ± 224.7	p = 0.043
Median [25%–75%]	189.0 [76.0–404.0]	307.5 [225.0–609.5]	86.0 [75.0–185.0]	
No. of exacerbation episodes in the year preceding therapy				
Mean ± SD	3.5 ± 3.3	7.1 ± 3.7	3.7 ± 0.8	p = 0.050
Median [25%–75%]	4.0 [3.0–6.0]	6.0 [5.5–9.5]	4.0 [3.0–4.0]	
Hospitalization in the year preceding therapy				
Yes/no	7/8	5/3	2/5	p = 0.315
ICS dose (in mcg of fluticasone)				
Mean ± SD	2306.7 ± 1047.6	2362.1 ± 1344.8	2242.9 ± 664.8	p = 0.954
Median [25%–75%]	2000 [1500–3000]	2000 [1250–3500]	2500 [1500–2750]	
OCS dose (in mg recalculated to prednisolone)				
Mean ± SD	9.5 ± 8.0	6.8 ± 4.9	12.7 ± 100	p = 0.266
Median [25%–75%]	8.0 [4.0–16.0]	6.0 [4.0–9.0]	12.0 [4.0–26.0]	
Diabetes	3/12	2/6	1/6	p = 1.000
Hypertension				
Yes/no	7/8	2/6	5/2	p = 0.132
Osteoporosis	5/10	2/6	3/4	p = 0.608

Characteristics of the study group

In total, 15 patients participated in the study: 4 males and 11 females. The mean dose of iGCS when recalculated to fluticasone was 2306 mcg. The mean dose of sGCS recalculated to methylprednisolone was 9.53 mg. The most common comorbidities included gastroesophageal reflux disease (GERD) – two patients, arterial hypertension – seven patients, type 2 diabetes – three patients, chronic sinusitis – seven patients, depression – three individuals, obesity – three patients and osteoporosis – five subjects (Table I). All the patients experienced within the year prior to inclusion to therapy three or more episodes of disease exacerbation that required intensified treatment consisting in administration of oral glucocorticosteroids (oGCS); all of them also reported significant deterioration of quality of life due to asthma (AQLQ below 5 points) and suffering from uncontrolled asthma (ACQ below 1.5 points). Seven patients were hospitalized during the past 12 months for asthma exacerbation; in four, persistent respiratory obturation was diagnosed and one individual had a documented episode of a life-threatening asthma attack. One subject was hypersensitive

to acetylsalicylic acid. Treatment effectiveness was evaluated after 16 weeks and one year following initiation of the treatment. The patients were divided into two groups according to their response to the treatment: a very good response (VGR) – eight patients and a good response (GR) – seven patients, based on the GETE scale (Table II). Initially there was not significant difference between the two groups in all evaluated parameters except the serum IgE level which was significantly higher in VGR group.

Table II – Global evaluation of treatment effectiveness scale

How effective omalizumab therapy is in improving of asthma control in patients?
Very good response: complete control of asthma – RESPONDER
Good response: significant improvement in asthma control – RESPONDER
Moderate response: marked but still limited improvement in asthma control
Poor response: lack of improvement in asthma control
Worsening: worsening in asthma control

Statistical analysis

All calculations were performed with STATISTICA 12 data analysis software system (StatSoft, Inc. Tulsa, Oklahoma, United States). Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean $\pm$ SD and median and lower and upper quartiles. Mann-Whitney and Wilcoxon tests were used for preliminary groups comparison. A general linear model (GLM) and a post hoc Tukey's test analysis were applied multiple groups comparison. A p value of less than 0.05 was considered statistically significant.

Results

At baseline, the patients divided later in two groups – GR and VGR – did not differ both in the AQLQ ($p = 1.000$) and ACQ scoring ($p = 1.000$) between the groups. After 16 weeks of therapy, ACQ decreased in the entire group by 21%, while after 12 months – by 34%. The observed changes in ACQ values were statistically significant as confirmed by the Wilcoxon test ($p = 0.023$ after 16 weeks and $p = 0.005$ after 12 months). During the follow-up observation, the VGR group showed a significant decrease in the ACQ scoring as early as after 16 weeks ($p = 0.015$) and an even more pronounced drop after 12 months ($p = 0.001$) as compared to the initial values. After 16 weeks, the decrease was 32%, while after 12 months – 51% (a statistically significant decrease $p = 0.012$ after 16 weeks and $p = 0.018$ after 12 months). In the GR group, changes in ACQ were statistically non-significant. In the latter group, only a tendency toward an ACQ decrease was noted (after 16 weeks, ACQ decreased by 8%, while after 12 months – by 10% ($p = 0.735$ and $p = 0.225$, respectively) (Fig. 1). In the entire treated group, changes in AQLQ as compared to the initial values were, respectively, as follows: an increase by 19% after 16 weeks of therapy, and by 34% after 12 months. The GR and VGR groups differed significantly also with respect to AQLQ. In the course of the

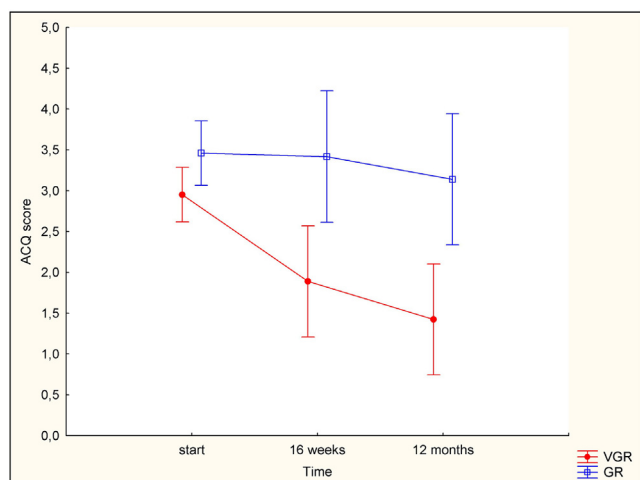


Fig. 1 – Changes in ACQ in both groups (VGR – red Line, GR – blue line) after 16 weeks and one year of therapy

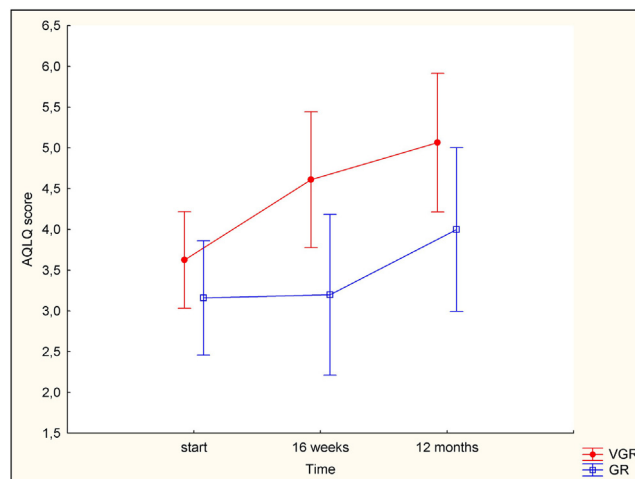


Fig. 2 – Changes in AQLQ in both groups (VGR – red Line, GR – blue line) after 16 weeks and one year of therapy

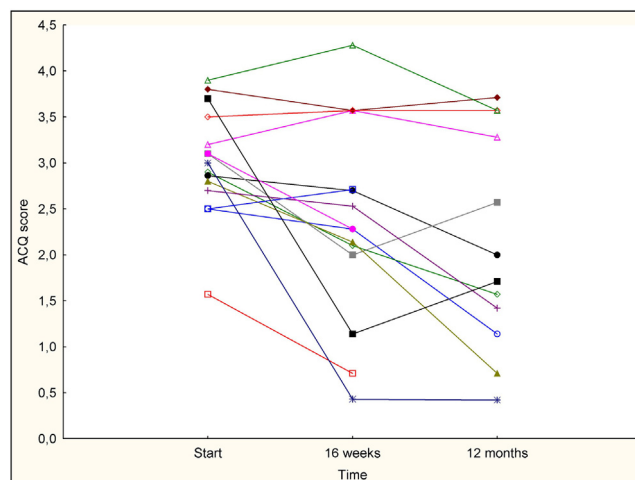


Fig. 3 – Changes in ACQ in the separate patients during OMA therapy

omalizumab therapy, in the VGR group, a significant increase in the AQLQ scoring was noted as early as in the 16th week ($p = 0.024$). The AQLQ scoring after 12 months increased even more ($p = 0.001$) as compared to the initial values (an increase of AQLQ by 31% after 16 weeks and by 40% after 12 months). In the group characterized by a good response (GR), changes in AQLQ were statistically non-significant (HSD $p = 1.000$ and $p = 0.168$, respectively). An increase of AQLQ was noted in this group as late as after 12 months, but it was statistically non-significant (Fig. 2). The courses of ACQ and AQLQ scores for separate patients are shown in Figures 3 and 4, respectively. The groups differed significantly in the FEV1 levels. In the VGR group, FEV1 was significantly higher as compared to the GR group (post hoc, $p = 0.025$). We observed a slightly different character of changes in FEV1 in the two groups in the course of the therapy. In the VGR group, we noted an increase of FEV1 at

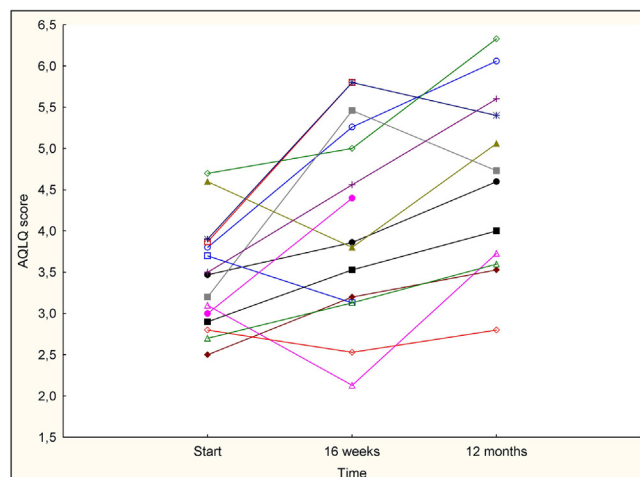


Fig. 4 – Changes in AQLQ in the entire group in the course of OMA therapy

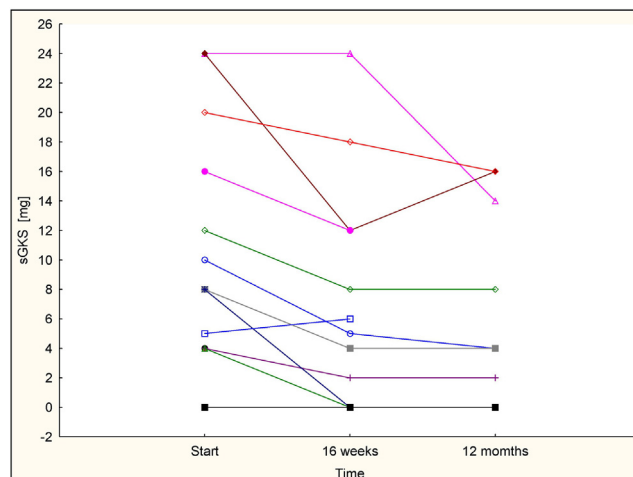


Fig. 5 – Changes in inhaled steroid dosage (taking into consideration particular patients) in the entire group in the course of OMA therapy

16 weeks, followed by a slight drop after 12 months. The GR group initially showed a small decrease of FEV1 at 16 weeks, followed by a moderate increase after 12 months. Interestingly, the patients characterized by a good response (GR) to the therapy demonstrated a lower initial level of FEV1 and the ultimate increase of FEV1 in this group was the highest. In the subjects who responded to the therapy very well, FEV1 was higher than in the GR group. Prior to the introduction of the therapy, in all the 15 patients, at least three episodes of disease exacerbation were documented in the year preceding OMA treatment. After 16 weeks, exacerbations were noted only in four out of 15 individuals (26.7%) and after one year, they were seen in 50% of the patients. While analyzing the decrease in the number of exacerbation episodes in the entire group, we observed a drop in the number of exacerbations by 92% after 16 weeks of the therapy and by 80% after 12 months. When the patients were divided into response-related subgroups, the VGR group demonstrated significant decreases in the number of exacerbations ($p = 0.012$ after 16 weeks and $p = 0.018$ after 12 months), while in the GR group, the decreases in the number of exacerbation episodes were significant after 16 weeks ($p = 0.018$) and after 12 months, $p = 0.068$, being close to statistical significance. After 16 weeks and after one year of the omalizumab treatment, the sGCS dose significantly decreased as compared to the initial value. When the patients were divided into the GR and VGR groups, a significant decrease of the sGCS dose was noted in the VGR group (after 16 weeks and after 12 months: $p = 0.018$ and $p = 0.028$, respectively). After 16 weeks, the GR group demonstrated a tendency toward a decrease of the sGCS dose ($p = 0.080$), while a statistically significant decrease of the sGCS dose was noted after 12 months of the therapy ($p = 0.043$) (Fig. 5). An analysis of the mean dose of iGCS demonstrated an increase in the iGCS dose on the omalizumab therapy in the entire group of patients. The fact resulted from an attempt made by physicians in some patients to taper the dose of systemic steroids at the cost of increasing the doses of inhaled steroids (Fig. 6).

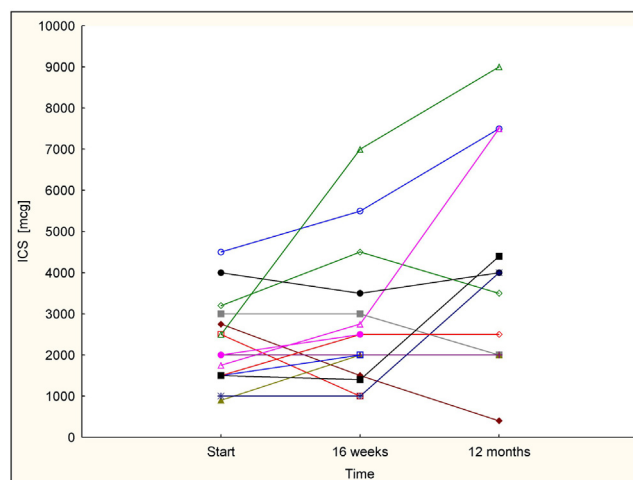


Fig. 6 – Changes of systemic steroids (taking into consideration particular patients) in the entire group in the course of OMA therapy

Discussion

Immunoglobulin E plays an important role in allergic diseases. It is produced by B lymphocytes, which in turn are activated by T helper type 2 cells (Th2). IgE binds to high-affinity receptors (Fc-epsilon-RI) that are present on basophils, mast cells, dendritic cells, and to low-affinity receptors (Fc-epsilonRII or CD23) on B lymphocytes, monocytes, macrophages and dendritic cells [6, 7]. IgE binding is followed by a release of a wide range of mediators, which are responsible for acute and chronic symptoms of allergic asthma. As IgE plays a central role in allergic asthma; no wonder it has become a target in therapy. The benefits and safety of omalizumab therapy has been shown in many studies. OMA decreases the levels of circulating IgE by binding to the constant region of the IgE molecule. The reduction in

circulating levels of IgE leads to downregulation of receptors on inflammatory cells, which results in extenuation of proinflammatory mediators.

To summarize the anti-inflammatory effects of OMA:

- It downregulates high-affinity receptors (Fc-epsilon-RI) present on basophils and mast cells [8, 9].
- It results in a marked reduction of serum IgE. It not only reduces the number of cells positive for the high-affinity Fc receptor for IgE in bronchial biopsies, but also CD3+, CD4+, and CD8+ T lymphocytes, B lymphocytes, and cells staining for interleukin-4, but does not result in an improvement in airway hyperresponsiveness to methacholine [10].
- After OMA administration, the production of IL-5 (Th2 cytokine, which is responsible for differentiation, proliferation and prolonging the life of eosinophils) by the peripheral blood mononuclear cells is decreased [11].
- Sputum eosinophils decrease [11, 12].
- Decreased bronchial tissue eosinophilia [10].
- Blood eosinophils decrease [9].

According to clinical outcomes, OMA decreases asthma exacerbations and the doses of oral or inhaled glucocorticoids [13]. Our knowledge of who will derive the greatest benefit from this therapy is still limited. Despite the fact that the patients meet the inclusion criteria in the program, we cannot predict with any certainty who will have a positive response. Some authors suggested impaired baseline lung function and frequent exacerbations as predictors of a good response to omalizumab [14]. The present study was carried out in the patients subject to more strict inclusion criteria in comparison to recommendations following from the summary of medicinal product characteristics (SmPC). Thus, comparing patients included into omalizumab therapy based on the SmPC and the National Health Insurance drug prescription program criteria is not possible. While analyzing the results of the present study, an attempt was made at finding a relationship between some indices prior to initiation of the treatment on the one hand and the response to therapy on the other. In a search for predictors of a very good response to omalizumab treatment, we analyzed spirometry parameters, age at asthma diagnosis and laboratory parameters. The initial IgE level was significantly higher in VGR group ($p = 0.018$) as compared to GR group. There was no significant relationship between age at asthma diagnosis, number of inclusion criteria met by the patient and response to treatment. The analysis of drug doses demonstrated a relationship at the borderline of statistical significance ($p = 0.084$). The patients better responding to the therapy were receiving a higher dose of omalizumab as compared to individuals showing a partial response to the treatment. Of statistical significance was the negative correlation between changes in ACQ and AQLQ at 16 weeks of treatment ($p = 0.010$). No significant correlation was noted between the number of inclusion criteria met by the patients and changes of ACQ and AQLQ in the course of treatment.

Conclusions

In properly qualified patients, one may expect a good or very good response to treatment. Our study has confirmed the publications to date that indicate effectiveness of

omalizumab in treatment of severe allergic asthma. Omalizumab has alleviated the symptoms, improved quality of life in patients with asthma; moreover, it helped to reduce asthma exacerbations and the use of systemic GCS. Employing the commonly available tools of evaluating asthma control and judging by initial parameters at initiation of treatment, it is not possible to conclude which patients will benefit more from omalizumab therapy. A tendency toward a better response has been noted in patients with a higher serum IgE concentration.

Authors' contributions/ Wkład autorów

AG-M – study design, data collection and interpretation, acceptance of final manuscript version, literature search. WZ – data collection, acceptance of final manuscript version, literature search. MP – data collection. AC – statistical analysis. KS – acceptance of final manuscript version.

Conflict of interest/ Konflikt interesu

None declared.

Financial support/ Finansowanie

A study based on the results of treatment in a therapeutic program of the National Health Fund./ Badanie przeprowadzone na podstawie wyników leczenia w programie terapeutycznym Narodowego Funduszu Zdrowia.

Ethics/ Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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