

# Loss of asthma control after cessation of omalizumab treatment: real life data

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Postep Derm Alergol 2014; XXXI, 1: 1–5

DOI: 10.5114/pdia.2014.40553

## Abstract

**Introduction:** Many clinical and observational studies have demonstrated effectiveness of omalizumab (OMA) in the treatment of severe asthma, but the optimal duration of the therapy remains unknown.

**Aim:** The article presents the authors' clinical experience on OMA cessation in routine practice.

**Material and methods:** Due to new reimbursement criteria, OMA therapy has been interrupted in 11 subjects (6 women/5 men). The mean age of patients was  $50.73 \pm 14.16$  years, the mean time of severe asthma duration was  $13.54 \pm 6.05$  years. All of them had an excellent/good response to OMA. The duration of OMA therapy was  $67.73 \pm 11.64$  months.

**Results:** Nine out of 11 patients had severe asthma exacerbation within the first 5 months after the OMA withdrawal. The mean time to the first severe exacerbation was  $7.56 \pm 2.67$  weeks. Between the time of OMA cessation and the time of reassessment, the mean score of Asthma Control Questionnaire increased from  $2.58 \pm 0.71$  to  $3.63 \pm 1.26$  points and the mean score of Asthma Quality of Life Questionnaire decreased from  $4.3 \pm 1.91$  to  $3.18 \pm 1.17$  points. The mean oral corticosteroids (OCS) dose increased from  $4.61 \pm 3.0$  mg/day to  $33.33 \pm 13.12$  mg/day. The number of exacerbations within the last 12 months increased from  $1.6 \pm 0.67$  to  $5.2 \pm 1.4$ , and the number of hospitalizations or emergency room (ER) attendance increased from  $0.11 \pm 0.31$  to  $1.56 \pm 1.26$ .

**Conclusions:** These data indicate that the withdrawal of OMA therapy after the successful long-term therapy may cause severe asthma exacerbations. Therefore, the decision regarding cessation of OMA treatment should be undertaken individually after careful weighing benefits and risks, especially in patients with a long history of severe asthma, treated with high doses of OCS before OMA introduction, near-fatal asthma events and/or aggravation of asthma during previous episodes of interruptions in OMA treatment.

**Key words:** severe asthma, discontinuation, omalizumab, asthma deterioration, exacerbations.

## Introduction

Although the majority of asthma patients can be effectively treated with inhaled corticosteroids (ICS) in monotherapy or in combination with long-acting  $\beta_2$ -agonists or leukotriene modifiers, a substantial subset of patients exists who do not respond even to high doses of ICS. These patients suffer from permanent asthma symptoms, experience limitation in life activity and have a low quality of life. They are at a high risk of severe asthma exacerbations and even fatal events. This group also accounts for a relatively large proportion of health care expenditure due to the direct and indirect costs [1].

Omalizumab is a humanized recombinant anti-IgE monoclonal antibody approved for the treatment of persistent severe (EU) or moderate-to-severe (USA) IgE-me-

diated asthma [2, 3]. Many clinical and observational studies have confirmed its effectiveness in improving asthma control, reducing rates of severe exacerbations and improving quality of life [4].

Due to the drug pharmacokinetics, the clinical effect is delayed. Omalizumab blocks free-circulating IgE inhibiting their binding to the specific receptors but does not displace them from the connection with specific receptors on target cells [5]. The clinical effect of omalizumab (OMA) on asthma control, based on the analysis of data from the INNOVATE study, begins from 12–16 weeks of treatment [6].

Though the onset of the drug action is already known, the optimal duration of the therapy still remains unknown. This study presents the authors' clinical experience on OMA cessation in routine practice.

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**Received:** 7.01.2014, **accepted:** 13.01.2014.

## Aim

The aim of the analysis was to evaluate asthma control after OMA cessation in patients previously treated with this drug over a period of 3 years and to characterize those patients who need continuation of treatment with OMA.

## Material and methods

Due to the introduction of new reimbursement criteria in the Polish Program of treatment of severe IgE-dependent asthma with OMA, funded by the national health insurance (Narodowy Fundusz Zdrowia – NFZ), OMA therapy had to be interrupted in some patients. All of them have been observed prospectively and subjected to the assessment of asthma control (Asthma Control Questionnaire – ACQ), quality of life (Asthma Quality of Life Questionnaire – AQLQ), the demand for anti-asthma agents (daily dose of oral corticosteroids in prednisone equivalent), the occurrence of severe exacerbations and the need for emergency medical care and hospitalization. The observations will be carried out until the therapy has been reintroduced. The analysis of changes in ACQ, AQLQ, daily dose of oral corticosteroids (OCS), number of hospitalization or emergency visits was performed in patients who were re-evaluated.

## Results

The analysis was performed among patients who interrupted the therapy between March 2013 (the start of the NFZ Program) and September 2013.

The therapy was discontinued in 11 patients (6 women/5 men) at the Department of Internal Medicine, Asthma and Allergy during that period. The mean age of patients was  $50.7 \pm 14.16$  years (min. 34 years, max. 70 years), the mean time of severe asthma duration was  $13.5 \pm 6.05$  years (min. 7 years, max. 27 years). All patients had an allergy to house dust mite, 6 to animal fur allergens, and 4 to molds and pollens. Monosensitization was detected in 3 subjects (all for mite). Six out of these 11 subjects had near-fatal asthma exacerbations recorded in their medical history.

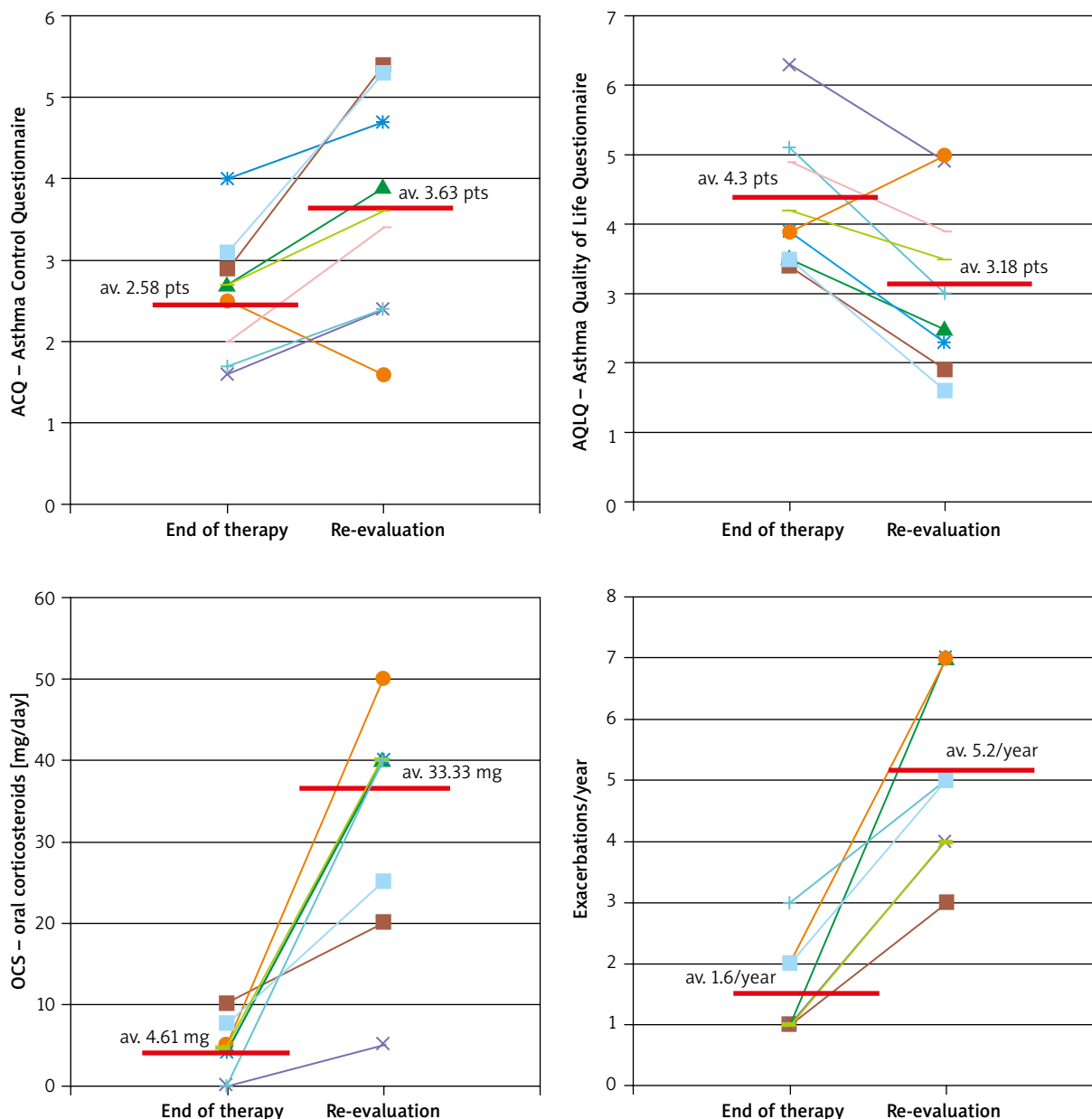
All patients received OMA due to severe allergic asthma, the dose was calculated according to the manufacturer's recommendations for asthma, the mean dose was  $422.73 \pm 262.3$  mg/month (min. 150 mg/month, max. 750 mg/month) (Table 1).

All patients responded to OMA therapy (according to the GETE scale (*Global Effectiveness Treatment Evaluation*), an excellent response was observed in 2 patients and a good response in the remaining subjects). The mean time from the initiation of OMA therapy to its cessation was  $67.73 \pm 11.64$  months. All patients since the beginning of treatment with OMA had occasional interruptions in therapy usually not exceeding 3 months due to the problems with reimbursement. The patients with the longest period of treatment in the first 2 years of therapy had an 11-month interruption for the same reason. Each time their asthma deteriorated and they experienced moderate to severe exacerbations. During the last year of therapy, patients received OMA regularly (except patient number 5 and 11 in Table 1) until the

**Table 1.** Baseline characteristics

Patient no.	Sex	Age	tIgE	Allergy	Duration of severe asthma	Near-fatal asthma	OMA dose/month	Duration of the therapy	Response to OMA	OCS/day before OMA	OCS/day during OMA (baseline for withdrawn)
1	M	35	482	M, Md, D, W	7	No	750	38	Excellent	5	0
2	F	67	308	M, C, D, T	15	No	600	65	Good	7.5	0
3	F	35	463	M	13	Yes	600	78	Good	20	0
4	M	61	51	M, T, W	14	No	150	78	Good	40	10
5	M	70	91	M	7	No	150	57	Excellent	10	0
6	F	54	91	M	9	No	150	66	Good	22.5	7.5
7	F	64	371	M, C	9	Yes	600	66	Good	20	5
8	F	37	325	M, C, D, T, G, W, Md	23	Yes	600	75	Good	25	5
9	M	38	30	M, T, G	13	Yes	300	78	Good	40	5
10	M	63	41	M, T	27	Yes	300	78	Good	20	5
11	F	34	93	M, T	12	Yes	150	66	Good	40	5
Av.	–	50.73	213.18	–	13.54	–	422.73	67.73	–	22.73	3.86
SD	–	14.16	169.28	–	6.05	–	262.30	11.64	–	12.18	3.26
Min.	–	34	30	–	7	–	150	38	–	7.5	0
Max.	–	70	482	–	27	–	750	78	–	40	10

M – mites, C – cat, D – dog, T – trees, W – weeds, G – grass, Md – molds, OMA – omalizumab, OCS – oral corticosteroids



**Figure 1.** Changes in ACQ, AQLQ, daily dose of OCS and number of severe exacerbations per year during the discontinuation of omalizumab – data for 9 patients

NFZ Program of severe asthma treatment with OMA was introduced.

Until the end of August 2013, the NFZ Program independent committee disqualified 11 patients from continuing OMA therapy because of the long duration of therapy (over 36 months).

Nine of these 11 patients had severe asthma exacerbations within the first 5 months after the OMA withdrawal. The mean time to the first severe exacerbation was 7.56 ±2.67 weeks. In all cases, visits to the emergency room (ER) or hospitalization were preceded by introducing or increasing the dose of OCS.

Since the time of OMA cessation to the time of patients' reassessment, the mean ACQ increased from 2.58 ±0.71 to 3.63 ±1.26 points, the mean AQLQ decreased from 4.3 ±1.91 to 3.18 ±1.17 points. The mean OCS dose (prednisone equivalent) increased from 4.61 ±3.0 mg/day to 33.33 ±13.12 mg/day. The number of exacerbations within the last 12 months increased from 1.6 ±0.67 to 5.2 ±1.4, and the number of hospitalizations or ER visits increased from 0.11 ±0.31 to 1.56 ±1.26 (Figure 1).

In 9 patients, OMA treatment has already been reintroduced (all subjects with a previous good response according to the GETE scale, none with an excellent

response), as they fulfilled inclusion criteria to the NFZ OMA treatment program. The mean time to reintroduction of OMA (after re-evaluation and checking the validity by the NFZ Program independent committee) was 17.22 ±3.64 weeks.

## Discussion

The majority of patients with diagnosed asthma suffer from mild-to-moderate disease which may be relatively well controlled by the use of standard therapy. However, 5% to 10% of patients have severe disease that is poorly controlled, even while taking the highest doses of antiasthmatic medications [7]. Although they represent a small proportion of patients, the social and economic costs of caring for them are high [8]. Omalizumab therapy is a recognized and recommended method of treatment of severe persistent allergic asthma in patients who are allergic to perennial allergens [9]. Pharmacoeconomic analyses have confirmed the cost-effectiveness of this method [10–12].

In Poland, approximately 1500 subjects have been estimated to suffer from severe persistent uncontrolled allergic asthma, and about 1000 could be treated with OMA [13].

Although the criteria for enrollment into the therapy with OMA and evaluation of its effectiveness are well established, the optimal duration of therapy is still unknown.

There are limited data on the asthma control after OMA therapy cessation. Corren *et al.* [14] evaluated the effect of OMA on skin reactivity to allergens and serum free IgE level during 28 weeks of therapy with high doses, then 18 weeks with reduced doses, and 8 weeks of follow up after cessation of therapy. They observed a reduction in serum free IgE level and immediate skin test reactivity to allergen during initial high-dose administration. These effects were not fully maintained during the dose reduction and returned to baseline after cessation of chronic treatment. The data analyses from the INNOVATE study reveal that OMA withdrawal after 28-week therapy leads to asthma symptom re-emergence, which correlates well with increasing free IgE and decreasing concentrations of the drug in serum [15].

From a theoretical point of view, the optimal time of therapy is 5 years. Lowe *et al.* calculated that regular treatment with OMA normalized IgE level in the 5<sup>th</sup> year of treatment based on the investigation of IgE concentration in 707 OMA treated patients, 745 from placebo group and 152 atopic but otherwise healthy subjects [16].

Almeida *et al.* [17] describe the case of a patient suffering from severe-resistant asthma who, after 1 year of successful therapy with OMA, stopped the treatment himself. In the next year, that patient had 10 asthma exacerbations, 4 of them requiring hospitalization, one of which with respiratory arrest. He improved clinically after restarting OMA treatment.

Molimard *et al.* [18] published the results of a retrospective observational study in severe asthmatic patients after discontinuation of OMA therapy. Data were collected from 61 patients (females 65.6%) whose mean age was 40.7 years (min. 6 years, max. 82 years). Mean asthma duration was 22.3 years and mean duration of OMA treatment was 22.7 months. After OMA discontinuation, median follow up duration was 9.26 months and loss of control was observed in 34 patients (55.7%). The highest rate and loss of asthma control were observed in the first year though they were still marked in the third year. Omalizumab was reintroduced in 20 out of 34 patients with loss of control, but 20% of them became non-responders despite previous sensitivity, which is a very worrying phenomenon.

The only 1 long-term study with a 6-year period of OMA treatment and a subsequent 3-year period of observation was a study by Nopp *et al.* [19]. Eighteen patients took part in the observation. All had severe asthma but none took persistently oral steroids before OMA introduction. All had a good response to OMA. One third of the patients lost asthma control after OMA cessation during 3 years of the observation.

In none of the above papers, the authors characterized groups of patients with long-lasting response and relapse of symptoms as well as exacerbations and analyzed the predictors of the permanent improvement in asthma control after OMA cessation. The individual patients' features and the course of the disease as well as the magnitude of response to OMA seem to be crucial for maintaining the good response after discontinuation of OMA.

Our data indicate that withdrawal of OMA therapy, after its successful long-term course, may cause severe asthma exacerbations in a certain group of patients. Our patients had a more severe disease than patients in the study by Nopp *et al.* [19], as they all permanently received oral steroids before OMA introduction. No data for comparison of asthma severity with Molimard *et al.* [18] study are available. All our patients had a long history of severe asthma, half of them near-fatal asthma attacks, only 2 achieved asthma control after OMA treatment even after oral steroids withdrawal. They all had occasional interruptions in therapy which resulted in asthma deterioration, but these with excellent results of OMA treatment had longer lasting control after OMA cessation and less severe exacerbations than others (no hospitalization or emergency visits, no course of oral steroids, or only short courses with low doses).

Based on the theoretical analysis, the standard optimal period of OMA treatment is closer to 5 years [16] than 3 years if the treatment is continued regularly as confirmed by the results of Nopp *et al.* [17], especially that there are the data on cost-effectiveness of this therapy up to 4 years [10].

Obviously, there is a group of patients who need OMA treatment for the rest of their lives, what is similar to management of people allergic to Hymenoptera venom with a high risk of anaphylaxis after discontinuation of allergy immunotherapy [20]. Omalizumab therapy should not be interrupted in these patients because of the high risk of severe life-threatening asthma exacerbations. Another argument against discontinuation of the therapy is the risk of secondary resistance to OMA, which is real as Molimard *et al.* [18] study showed. Therefore, every time a decision regarding cessation of OMA treatment should be undertaken individually after careful weighing of benefits and risks, especially in patients with a long history of severe asthma, treated with high doses of OCS before OMA introduction, near-fatal asthma events and/or aggravation of asthma during previous episodes of interruptions in OMA treatment.

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