

Small, Prospective, Observational, Pilot Study in Patients with Severe Asthma after Discontinuation of Omalizumab Treatment

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ABSTRACT

Purpose: Omalizumab has demonstrated clinical efficacy in severe allergic asthma by reducing exacerbation rates and increasing quality of life. However, data concerning its sustained effect after treatment discontinuation are still needed.

Methods: : This analysis was an observational pilot study (simple within-subjects design) of 12 patients experiencing severe asthma, treated with omalizumab, for 1 year after treatment discontinuation. We prospectively analyzed clinical measurements (pulmonary functions, inhaled corticosteroid [ICS] doses, Asthma Control Test [ACT] scores, skin prick test [SPT] positivity, fraction of exhaled nitric oxide, and exacerbation rates) and laboratory test results (eosinophils and total immunoglobulin E levels) at the time of discontinuation and 6 and 12 months thereafter. Baseline data (before the treatment period; range, 11–61 months) were collected retrospectively. The treatment effect until discontinuation was calculated. To determine its persistence, repeated measures were compared with baseline levels and analyzed by using a general linear model for repeated measures or the Friedman ANOVA, and χ^2 tests in case of normality assumption violation or frequencies. Post hoc analysis was applied by using a simple or repeated contrasts analysis or Wilcoxon signed rank test with Bonferroni correction.

Findings: : We proved a significant reduction in ICS doses and SPT reactivity and an increase in ACT score during the retrospective treatment phase. Moreover, persistence of these statistically significant effects was recorded 6 months after treatment discontinuation. ACT score and ICS doses (but not SPT reactivity) remained improved for 12 months after discontinuation of omalizumab treatment.

Implications: Omalizumab treatment exhibited sustained treatment benefit after its discontinuation for patients experiencing severe allergic asthma. (*Clin Ther.* 2018; 40:XXX–XXX) © 2018 Elsevier HS Journals, Inc. (*Clin Ther.* 2018;■:1–12) © 2018 Elsevier Inc. All rights reserved.

Key words: Asthma Control Test, inhaled corticosteroids, omalizumab, severe asthma, skin prick test.

INTRODUCTION

Asthma is a heterogeneous disease, usually associated with airway inflammation and hyperreactivity. Severe asthma or therapy-resistant asthma is one of the major unmet needs associated with a chronic progressive course, leading to a loss of pulmonary functions, airway remodeling, and propensity to severe exacerbations.¹ Extraordinary efforts are being made to discover the biological nature of the disease, especially in terms of the exact role of inflammation and tissue remodeling.^{2,3}

Despite an enhanced understanding of asthma pathophysiology, the ideal treatment of severe asthma remains elusive.⁴ Together with such investigations, a need has arisen for more rigorous disease classification as well as a description of those patients who best respond to evolving biologic agents. New biomarkers may be the key to more precision medicine.⁵

Omalizumab (OMA) is a recombinant humanized anti-immunoglobulin E (IgE) antibody approved by

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the US Food and Drug Administration in 2003 for the treatment of severe allergic asthma inadequately controlled despite optimal controller therapy. Two years later, it was approved in the European Union, and it has found its place in the asthma treatment algorithm of the Global Initiative for Asthma (GINA) Guidelines as well.⁶ In 2014, the GINA update newly recommended OMA for asthma treatment even before the use of oral corticotherapy.⁷ To date, OMA has been used in the Czech Republic for the treatment of patients experiencing severe refractory asthma in 8 centers for the biologic treatment of severe asthma for >10 years. Allergists and pulmonologists collaborate in these centers, with the goal of determining all eligible patients with asthma most likely to benefit from this biologic therapy and evaluating the real-world clinical effect.

Despite high-quality pharmacokinetic and pharmacodynamic data confirming the clinical benefit of OMA treatment,^{8–11} we still lack a practical and readily available way to estimate the clinical response to OMA therapy except for baseline total IgE level measurement and 16-week treatment trial.^{12,13} Bousquet et al.¹⁴ reported that a longer assessment period may be more valuable in a small fraction of patients. These practical difficulties become even more challenging when we speculate about step-down OMA therapy in patients who have attained clinically stable disease.

A number of randomized, double-blind clinical trials, as well as many observational real-world studies, have confirmed the long-term efficacy of OMA in improving clinical outcomes.^{15,16} However, the optimal duration of therapy and the potential persistent clinical effect after OMA discontinuation are unclear. Moreover, the conceivable effect of OMA on the natural history of asthma and on airway remodeling remains elusive.^{17,18}

To date, sound evidence exists that the reduction in free IgE levels after anti-IgE therapy leads to reductions in high-affinity IgE receptor (FcεRI) expression on mast cells, basophils, and dendritic cells,¹⁹ attenuation of several markers of inflammation, including peripheral and bronchial tissue eosinophilia, and levels of several cytokines. This immunomodulatory activity has broad clinical effects, including a reduction in the severe exacerbation rate and fewer visits to the emergency department or even less probable hospitalization due to asthma worsening.^{17,20,21}

There are also rare reports that anti-IgE therapy suppresses skin reactions,^{22–24} as well as other clinical manifestations of allergic reactivity^{24,25} or susceptibility to viral infections.²⁶ It is plausible that therapy targeting IgE may influence the natural history of the disease and potentially the remodeling process as well.^{18,27–29} All these facts open up the question of a conceivable sustained effect of OMA after its cessation.

One long-term study highlighted the possible role of anti-IgE therapy in improving the course of asthma, with clinical improvements that continued to be observed 3 years after withdrawal of long-lasting (6 years) treatment.^{30,31} However, other clinical observations suggest an increased risk of severe asthma exacerbation during the first year after OMA discontinuation or even upon dose reduction.^{32–34}

In view of this clinically challenging issue, we have prospectively analyzed the clinical and laboratory findings of 12 patients treated with OMA in the center for biologic treatment of severe asthma in the Institute of Clinical Immunology and Allergy (University Hospital, Hradec Králové, Czech Republic) over a 1-year period after treatment was discontinued because clinical stability had been achieved.

PATIENTS AND METHODS

Study Objectives and Design

This study was a prospective, longitudinal, observational, single-arm, open-label trial (2010–2015) to assess the duration of the clinical effect of OMA treatment after its discontinuation. For this purpose, we analyzed the clinical and laboratory findings of patients with asthma for 1 year after OMA treatment discontinuation based on patient's personal reasons, concurrently assuming achieved clinical stability. All evaluated parameters are routinely acquired in our center in all patients undergoing initial evaluation for OMA treatment suitability.

The study had a simple within-subjects design consisting of 2 phases: retrospective and prospective. During the first retrospective phase, an effect of OMA treatment was calculated by comparing the actual measured data at the treatment discontinuation with patients' retrospectively collected baseline counterparts measured before the treatment initiation (T0). In the following prospective

phase, repeated measures were provided at 2 additional time points, 6 and 12 months thereafter (T6 and T12). The retrospectively analyzed treatment duration varied in particular patients; the follow-up prospective period had a specific timing framework. The study design is reviewed in [Figure 1](#).

Study Subjects and Inclusion Criteria

The study group consisted of 12 patients (6 men, 6 women; age range, 22–58 years) fulfilling all local indication criteria for treatment with OMA³⁵ (severe allergic asthma,¹ uncontrolled despite treatment with high-dose inhaled corticosteroids [ICS] and long-acting beta-agonists, satisfyingly treated comorbidities such as allergic rhinitis, rhinosinusitis with or without nasal polyps, gastroesophageal reflux disease, sleep apnea syndrome treated according to national guidelines, acceptable intention to undergo treatment [including good compliance with treatment procedures, constantly avoiding smoking, and educated regarding inhalation techniques], ≥ 2 severe asthma exacerbations^{36,37} in the previous year, and sensitization for at least 1 perennial allergen). All patients were recognized as good responders to OMA therapy (defined as marked improvement of asthma control and reduction of severe exacerbations assessed by a physician after 16 weeks of treatment).¹² Moreover, all included subjects had personal reasons for discontinuing OMA treatment and concurrently confirmed clinical stability of the disease

during the 6-month period before deemed OMA discontinuation. Clinical stability of disease was defined as fulfillment of both the following criteria: (1) absence of severe exacerbation; and (2) Asthma Control Test (ACT) score ≥ 20 points at most of their visits.

All patients were managed at the center for biologic treatment of severe asthma using OMA as add-on therapy, and they underwent the entire study protocol with no loss of follow-up.

Due to lack of recommendations concerning OMA treatment duration or indications for its withdrawal, the decision regarding OMA discontinuation was based on the patient's voluntary wish for personal reasons and required mutual agreement between the patient and his or her physician assuming clinical stability of the disease (defined earlier). All patients were followed up according to a standard visit regimen and managed according to standard conventional treatment of severe bronchial asthma. The study group's demographic characteristics are summarized in [Table I](#). Due to the noninterventional nature of the study, no informed consent was necessary according to local ethics committee requirements. The local ethics committee stated a favorable opinion of the study design (Reference No.: 201709S17).

Clinical and Laboratory Procedures

All patients underwent a clinical examination at each study visit, including: spirometry,³⁸ determined

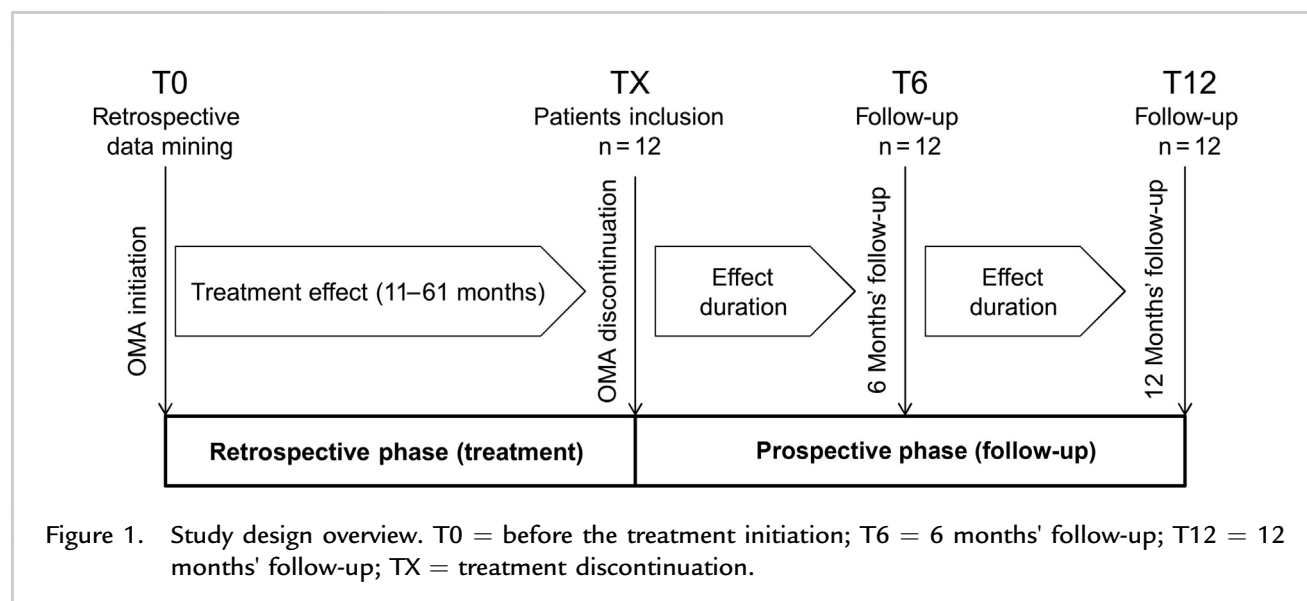


Table I. Baseline demographic characteristics of the study subjects.

Characteristic	Mean (SD)	Range
Age	40.6 (9.2)	29–58
Weight, kg	78.4 (15.1)	59–104
Height, cm	171.8 (11.7)	155–196
Body mass index, kg/m ²	26.1 (3.2)	23.3–32.7
FEV ₁ (% of predicted)	68.4 (11.4)	50.3–83.3
FEV ₁ /VC _{max}	67.7 (8.4)	58.7–78.2
ACT score, points	15.1 (3.72)	5–19
FeNO, ppb	56.4 (35.4)	10–109
Total IgE, IU/mL	402.1 (371.9)	53–1294
Absolute eosinophil count, eosinophils/ μ L	335.8 (192.9)	53–650
ICS (BUD equivalent), μ g/d	1782 (629)	1200–3200
Omalizumab therapy duration, mo	29.5 (16.1)	11–61
Omalizumab dose, mg/mo	457 (318.7)	150–1200

ACT = Asthma Control Test; BUD = budesonide; FEV₁ = volume of air exhaled during the first second of forced exhalation; FeNO = fractional concentration of exhaled nitric oxide; ICS = inhaled corticosteroid; IgE = immunoglobulin E; ppb = the number of particles per billion; VC_{max} = maximal vital capacity.

as the volume of air exhaled during the first second of forced exhalation (FEV₁; expressed in % of predicted values) and the ratio of FEV₁ and maximal vital capacity (VC_{max} [FEV₁/VC_{max}]; Jaeger MasterScreen, CareFusion Germany 234 GmbH, Höchberg, Germany), with the examination performed in a certified lung function testing laboratory at the Institute of Clinical Immunology and Allergy; analysis of nitric oxide production in exhaled breath (FeNO); relative fraction of nitric oxide in exhaled breath expressed in the number of particles per billion^{39,40} (HypAir FeNO, Medisoft, Sorinnes, Belgium), with the examination performed in a certified lung function testing laboratory at the Institute of Clinical Immunology and Allergy; and skin prick tests (SPTs; Alyostal, Stallergenes Greer, London, United Kingdom), with positivity defined as mean wheal diameter ≥ 3 mm. The individual dominant allergen was described before initiation of OMA treatment (primary allergen was determined according to the most dominant SPT and/or specific IgE positivity in correlation to clinical relevance), and its longitudinal positivity in SPT was monitored during the entire study period. SPT positivity was expressed categorically according to the mean wheal reaction diameter in 4 groups (1 = mean wheal

diameter 3–5 mm; 2 = >5–10 mm; 3 = >10–15 mm; and 4 = >15 mm).

A medical history of daily doses (DD) of ICS (assessed and expressed as equivalent doses to budesonide) and severe asthma exacerbations³⁷ was recorded, and an Asthma Control Test (ACT) questionnaire was administered. An improvement of ≥ 3 units on the ACT score is considered to be the minimal important difference.^{41,42}

Blood samples were taken to determine the absolute eosinophil count, and total IgE levels were assessed. The levels of specific IgE were measured only before treatment initiation to confirm dominant allergen linkage. All laboratory tests were performed in a certified laboratory at the Institute of Clinical Immunology and Allergy.

Primary and Secondary Outcomes

The primary outcome was to assess the stability of clinical and laboratory improvements, resulting from OMA treatment, after therapy discontinuation. To meet this objective, we had to define variables displaying significant changes during the treatment period itself (retrospective phase, treatment discontinuation vs T0). Thereafter, we tested the sustainability of these calculated improvements

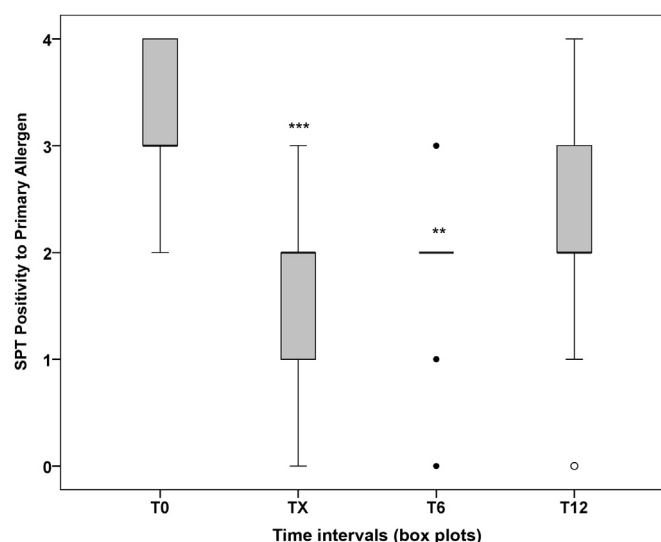


Figure 2. Time-dependent changes in categorical skin prick test (SPT) positivity for dominant allergen. Positivity expressed categorically according to mean wheal diameters: 1, 3 to 5 mm; 2, >5 to 10 mm; 3, >10 to 15 mm; and 4, >15 mm. Friedman ANOVA $\chi^2(11) = 23.01$, $P < 0.001$; Kendall's coefficient of concordance $W = 0.7$, post hoc Wilcoxon signed rank test with Bonferroni correction. T0 = before the treatment initiation; T6 = 6 months' follow-up; T12 = 12 months' follow-up; TX = treatment discontinuation. *** = $P < 0.001$, ** = $P < 0.01$.

during the prospective follow-up period (6 months vs T0 and 12 months vs T0).

For these purposes, we repeatedly assessed clinical (pulmonary functions, SPT, history of exacerbations, and ACT scores) and laboratory (FeNO, serum total IgE, and absolute eosinophil count) measures immediately after treatment discontinuation and during the follow-up phase, up to 12 months. Baseline levels of particular measures were collected retrospectively from the center's medical documentation.

A secondary outcome was to investigate the dynamics of clinical progress during the treatment and the follow-up phase by using statistical modeling.

Statistical Analysis

Descriptive statistics are expressed as means and SDs or as medians and interquartile ranges in cases in which the normal data distribution assumption has not been met or in cases concerning categorical data.

Repeated measures were treated by using a general linear model for repeated measures (GLM-RM) or the Friedman ANOVA in cases of normality assumption violation. Frequencies were analyzed by using the χ^2 test.

Post hoc analysis was assessed by using simple contrasts or the Wilcoxon signed rank test with Bonferroni correction. Standardized effect size was calculated by using partial η^2 for GLM-RM or Kendall's coefficient of concordance W for the Friedman ANOVA, respectively. P values < 0.05 were considered statistically significant. Data were analyzed by using IBM SPSS Statistics for Windows version 22.0 (IBM Corporation, Armonk, New York).

RESULTS

Treatment Period

Mean OMA therapy duration was 29.5 months (range, 11–61 months) with a recommended dosing scheme according to total IgE level and weight. The mean OMA dose was 457 mg per month (range, 150–1200 mg). Two patients were prescribed oral corticosteroids as maintenance therapy. All included patients were nonsmokers and with no other concurrent pulmonary pathology.

Clinical Outcomes

OMA treatment did not significantly change pulmonary function (FEV_1 , $P = 0.454$; FEV_1/VC_{max} ,

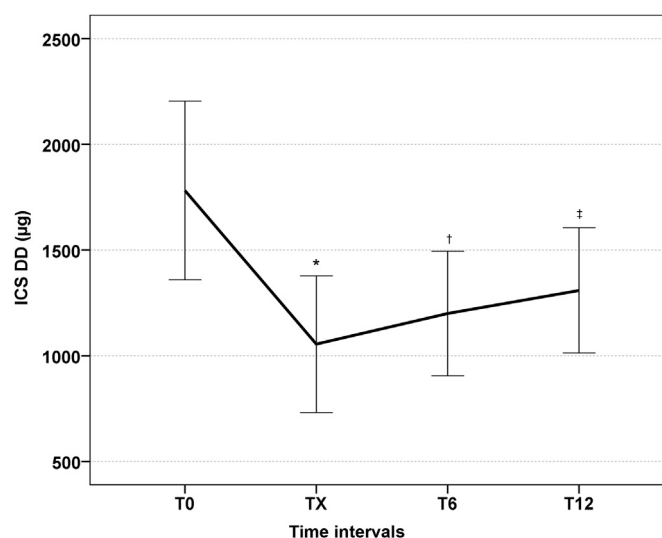


Figure 3. Time-dependent changes in inhaled corticosteroid (ICS) daily doses (budesonide equivalent). Variable expressed as mean with 95% CI, general linear model for repeated measures, ANOVA $F(3.30) = 11.8$, $P < 0.001$, partial $\eta^2 = 0.54$, simple contrasts, $*P < 0.001$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.05$. T0 = before the treatment initiation; T6 = 6 months' follow-up; T12 = 12 months' follow-up; TX = treatment discontinuation.

$P = 0.48$) in any patient, and we observed no significant worsening during the follow-up phase.

However, an obvious clinical improvement was noted in the elimination of severe asthma exacerbations. The mean baseline retrospective exacerbation rate was 2.5 per 1 year per patient. We recorded no severe exacerbations in any patient during the OMA treatment period ($P < 0.001$), and overall only 2 severe exacerbations (each in 1 patient) occurred during the 1 year after treatment discontinuation follow-up (6 and 12 months after treatment cessation, respectively; $P < 0.001$).

FeNO levels at OMA treatment initiation decreased nonsignificantly during the treatment period and for 1 year after treatment discontinuation ($P = 0.121$).

A clinically and statistically significant reduction was observed in reactions in SPTs to the dominant allergen during OMA treatment and immediately after its discontinuation ($P = 0.001$, Kendall's $W = 0.7$). This effect remained statistically significant for the primary allergen 6 months after therapy discontinuation ($P = 0.002$; omnibus ANOVA for general effect, $P < 0.001$) and was independent of respective allergen linkage and of all the other

analyzed clinical parameters, including OMA dose and duration of therapy. Time-dependent changes in SPT positivity are expressed in Figure 2.

ICS DD (budesonide equivalent) was permanently tapered during OMA treatment ($P < 0.001$) and even 12 months after therapy cessation ($P = 0.001$; GLM RM, $P < 0.001$, partial $\eta^2 = 0.54$). This effect was independent of patient sex, age, weight, body mass index, pulmonary functions (FEV_1 and FEV_1/VC_{max}), initial dose of ICS, initial ACT score, FeNO, total IgE, absolute eosinophil count, OMA monthly dose, OMA treatment duration, and type of primary or secondary sensitization (nonsignificant result of analysis of interaction effects). Two patients were treated with oral corticosteroids before OMA therapy initiation, and the corticosteroids were then withdrawn from treatment permanently. The time-dependent changes in ICS DD are shown in Figure 3.

The score of the respective ACT improved significantly during OMA treatment ($P < 0.001$) and remained thus even 12 months after therapy discontinuation ($P = 0.002$) (omnibus ANOVA, $P < 0.001$; Kendall's $W = 0.8$). No patient reported a decreased symptom score. A reduction in ICS DD

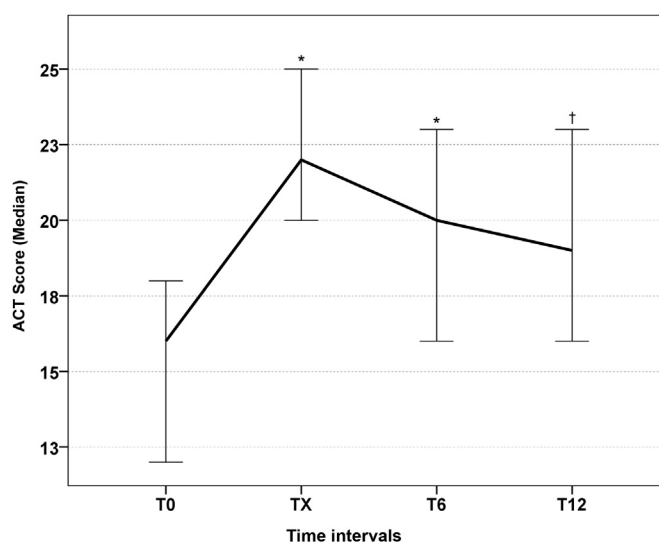


Figure 4. Time-dependent changes in Asthma Control Test (ACT) score. Variable expressed as median with 95% CI, Friedman ANOVA χ^2 (11) = 24.4, $P < 0.001$, Kendall's $W = 0.8$, post hoc Wilcoxon signed rank test with Bonferroni correction, * $P < 0.001$, † $P < 0.01$. T0 = before the treatment initiation; T6 = 6 months' follow-up; T12 = 12 months' follow-up; TX = treatment discontinuation.

was in inverse relation to the changes in ACT scores. Analysis of interaction effects revealed insignificant results with regard to all of the clinical factors assessed. The results of ACT time-dependent changes are shown in Figure 4.

Laboratory Outcomes

The total IgE level increased significantly ($P < 0.001$) throughout the entire treatment period and returned to its initial range 6 months after therapy discontinuation (omnibus ANOVA, $P < 0.001$; Kendall's $W = 0.64$). The absolute eosinophil count decreased nonsignificantly during the treatment period and did not increase after OMA discontinuation ($P = 0.337$). The results of clinical and laboratory measurements are reviewed in Table II.

DISCUSSION

Asthma is a highly heterogeneous disease involving a complex of pathologic mechanisms.⁷ A large volume of evidence has indicated that the inflammatory cascade could be activated by binding IgE to FcεRI that are present in the surface of mast cells and basophils.⁴³ It has been established that the presence of IgE could up-regulate FcεRI expression on effector cells.⁴⁴

OMA specifically binds to the circulating IgE by occupation of the Cε3 region of the free IgE. This interaction subsequently inhibits its binding to the high-affinity receptor⁴⁵ and lowers the FcεRI expression on mast cells and basophils, thereby interrupting the inflammatory cascade and the release of proinflammatory mediators.⁴⁶

Lowe and Renard⁸ found that IgE production is regulated by a free IgE and correlates with changes in total IgE concentration in patients undergoing long-term OMA treatment. They estimated that OMA reduces IgE production by 54% per year, and patients are expected to have an IgE level that approximates that of a healthy individual following 5 to 6 years of OMA treatment. This finding supports the observations of a Swedish study that analyzed a small number of patients treated with OMA for a 6-year period and reported a clinical benefit for a period of 3 years after withdrawal.^{30,31}

Several other studies have evaluated asthma control after short-term OMA treatment discontinuation. Slavin et al.³⁴ analyzed the follow-up data from the INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) clinical study and noted an increased risk of symptom relapse early after OMA

Table II. Analysis of time-dependent outcomes.

Variable	T0	TX	T6	T12	<i>P</i>
	OMA Treatment Period		Follow-up Period		
ITT, no.	12	12	12	12	
Severe exacerbations					
Frequency per patient per year	2.5	0 [*]	0.08 [*]	0.17 [*]	<0.001 [†]
FEV ₁ (% of predicted)					
Mean	68,4	68,7	68	66,8	
SD	11,40	13	10,4	10,3	0.454 [‡]
FeNO, ppb					
Median	61	35	28	30	
IQR	24–90	15–42	20–70	22–49	0.121 [§]
SPT (categorical degrees)					
Median	3	2 [*]	2	2	
IQR	3–4	1–2	2–2	2–3	<0.001 [§]
ICS DD (BUD equivalent), µg					
Mean	1782	1055 [*]	1200	1309 [¶]	
SD	629	482	438	441	<0.001 [‡]
ACT score (points)					
Median	16	22 [*]	20 [*]	19	
IQR	14–18	20–23	19–23	17–23	<0.001 [§]
Total IgE, IU/mL					
Median	266	393	230	182	
IQR	105–616	198–939	120–804	89–802	<0.001 [§]
AEC, eos/µl					
Median	300	260	300	330	
IQR	170–550	170–500	260–500	280–580	0.337 [§]

ACT = Asthma Control Test; AEC = absolute eosinophil count; BUD = budesonide; eos = eosinophils; FEV₁ = volume of air exhaled during the first second of forced exhalation; IQR = interquartile range; ITT = intention-to-treat; ppb = the number of particles per billion; T0 = before the treatment initiation; T6 = 6 months' follow-up; T12 = 12 months' follow-up; TX = treatment discontinuation.

* $P < 0.001$.

[†] χ^2 test.

[‡] General linear model for repeated measures (post hoc repeated contrasts, reference interval T0).

[§] Friedman ANOVA (post hoc Wilcoxon signed rank test with Bonferroni correction, reference interval T0).

[¶] $P < 0.05$.

^{||} $P < 0.01$.

treatment cessation (28 weeks of treatment and 16 weeks of follow-up), correlating with an IgE level increase noted even 6 months after OMA withdrawal. Similarly, Corren et al.²³ reported a quick relapse of SPT reactivity after OMA treatment dose reduction or termination. A Polish group has reported that some patients exhibit a gradual worsening of asthma control and an increase in

exacerbation risk after only a short period (7.56 [2.67] weeks) following cessation of OMA treatment.^{32,47} However, a positive correlation between treatment duration and sustained asthma control was noted in another study by Molimard et al.³³ OMA treatment discontinuation after almost 2 years (22.7 [13.1] months) in 61 patients led to a worsening of asthma control in 55.7% (34 of 61) of

the patients (mean time to loss of control, 20.4 [13.1] months).

Busse et al.⁴⁸ conducted (2010–2013) a Phase IV, multinational, randomized, placebo-controlled clinical trial (XPORT [Evaluating Xolair Persistency of Response After Long-Term Therapy]) primarily aimed at evaluating the persistency of response to OMA in patients with moderate to severe asthma (52 weeks after OMA therapy discontinuation). Preliminary results found that nearly 40% of the patients remained free of severe asthma exacerbation after 1 year of discontinuing long-term OMA treatment. Definite results confirmed the existence of a substantial group of responders who tend to benefit from OMA therapy, despite that the adjusted odds ratio (age, sex, ICS use) of continuing OMA treatment for risk of acute exacerbation was 0.44 (95% CI, 0.23–0.82).⁴⁹

In the present study data, we observed a sustained effect of OMA therapy even 1 year after therapy discontinuation. The differences in our study results compared with the studies performed by the Polish group^{32,47} and Slavin et al.,³⁴ both showing an early loss of asthma control after OMA therapy discontinuation, may be a result of differences in distinct study samples. Our patients tended to have a milder form of severe asthma (in contrast to that of the patients in the study by Kupryś-Lipińska and Kuna³²), and the treatment duration was substantially longer than that described in the study by Slavin et al. However, our findings seem to be in concordance with results and statements of Nopp et al.,³⁰ Molimard et al.,³³ and at least partly with the results of Busse et al.⁴⁸ and Ledford et al.⁴⁹

The main goal of the present study was to determine the duration of effect of OMA therapy after its discontinuation. The disadvantage of this study is the absence of a placebo control arm during the treatment period and during the follow-up phase, a small sample size, and the absence of randomization and blinding. These limitations result from the real-life nature of this study.

Future research on this topic is highly anticipated and required because the step-down approach in cases of biologic therapy of asthma is still not advocated in international or local guidelines, despite its practical impact and need. It therefore remains a delicate issue to decide whether to discontinue a well-established therapy after achievement of disease

stability. This fact almost precludes an option of randomization and antecedent power analysis, especially in real-life studies. Thus, only a limited number of studies address this issue and, to the best of our knowledge, only 1 randomized controlled trial has been published.⁴⁹ Moreover, the inclusion criteria for OMA treatment initiation vary across different countries, and thus the results can be compared only with difficulty.

Conversely, a small sample size with a low statistical power increases the probability of a type II error, and reaching statistical significance therefore requires more relevant clinical impact.

We conceived this clinical trial as a pilot study, and we are planning an extension of the study sample by including a National Registry file of patients with severe asthma treated with biologic therapy in the Czech Republic.

CONCLUSIONS

The present study found a significant reduction in ICS DD and SPT positivity and an increase in ACT score during OMA treatment, regardless of the dominant allergic linkage, treatment duration, or OMA dose. This effect on the ICS dose and ACT score was evident even 12 months after treatment discontinuation. The reduction of primary allergen SPT was significant 6 months after therapy discontinuation.

We concluded that OMA therapy may affect the clinical outcome even 1 year after therapy discontinuation. The “step down” of omalizumab in “treatment responders” remains a highly individual process that can be implemented subject to mutual agreement with the patient under a clearly defined treatment plan.

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Irena Krčmová was responsible for study design, data collection, interpretation and manuscript preparation. Jakub Novosad was responsible for data collection, statistical analysis and interpretation,

figure creation and manuscript preparation. Eva Malá and Jan Krejssek contributed to manuscript preparation and results interpretation.

CONFLICTS OF INTEREST

Monetary support (grant PROGRESS Q40) was used only for reimbursement of material in laboratory analysis and did not result in any conflict of interest. The authors have no conflicts of interest regarding the content of this article.

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