

Long-term efficacy and safety of omalizumab in patients with allergic asthma: A real-life study

Andriana I. Papaioannou, M.D., Ph.D.,¹ Myrto Mplizou, M.D.,¹ Konstantinos Porpodis, As. Prof.,² Evangelia Fouka, M.D., Ph.D.,² Eleftherios Zervas, M.D.,³ Konstantinos Samitas, M.D., Ph.D.,³ Miltiadis Markatos, M.D.,⁴ Petros Bakakos, M.D.,⁵ Spyridon Papiris, Ph.D.,¹ Mina Gaga, M.D., Ph.D.,³ Despoina Papakosta, Ph.D.,² and Stelios Loukides, Ph.D.¹

ABSTRACT

Background: The efficacy and safety of omalizumab in patients with severe allergic asthma have been established in both randomized controlled trials and real-life studies.

Objective: To evaluate the sustained effectiveness and safety of long-term treatment with omalizumab in a real-world setting.

Methods: In this retrospective study, we included patients treated with omalizumab for at least 8 years in four asthma clinics in Greece. Pulmonary function, asthma control, oral corticosteroids (OCS) dose, and exacerbations were recorded before treatment, 6 months later, and annually thereafter. Adverse events were also recorded.

Results: Forty-five patients (66.7% women), mean $\pm$ standard deviation (SD) age 55.3 ± 12.2 years, were included. The duration of treatment with omalizumab was 10.6 ± 1.2 years. The annual exacerbation rate decreased from 4.1 before omalizumab initiation to 1.1 after 1 year of treatment and remained low up to the 8th year of treatment ($p < 0.001$). From the 19 patients who were receiving OCS at baseline, 21.1% patients discontinued after 6 months, 47.4% were still on OCS after 4 years of therapy, and 31.6% were on OCS after 8 years. With regard to the OCS dose, 36.8% of the patients reduced the dose $\geq 50\%$ after 6 months and 68.4% achieved 50% reduction after 2 years. The mean daily OCS dose before omalizumab initiation was 7.8 mg of prednisolone or the equivalent, reduced to 4.7 mg/day after 6 months, which reached 1.6 mg/day after 8 years ($p < 0.001$). Treatment with omalizumab resulted in significant improvements of asthma control and lung function. No severe adverse events were reported.

Conclusion: In this real-life study, omalizumab resulted in significant and sustained improvements in asthma exacerbations, asthma control, and lung function, and had a steroid sparing effect and a good safety profile.

(Allergy Asthma Proc 42:235–242, 2021; doi: 10.2500/aap.2021.42.210014)

Asthma is a heterogeneous disease characterized by different clinical and pathophysiologic profiles.¹ Despite the development of potential treatments, asthma is still a major public health concern that affects

235 million people worldwide.² Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent the asthma from becoming uncontrolled, or that remains uncontrolled despite this therapy.³ Although the prevalence of severe asthma is estimated at ~ 5 –10% of patients with asthma, it accounts for $> 50\%$ of the global costs of asthma, which makes it a clinical and social problem.^{4–6} Severe asthma is also heterogeneous and includes several phenotypes.¹ In 50–80% of patients with asthma, allergic mechanisms are implicated, and these percentages are also applicable to the population of those patients with severe asthma.^{7–10} In allergic asthma, immunoglobulin E (IgE) binds to the Fc region of the high affinity (Fc ϵ RI) receptor on the surface of mast cells and basophils, and the low affinity (Fc ϵ RII) receptors on B lymphocytes, which results in the activation of an allergic cascade and the development of asthma symptoms.¹¹

Omalizumab is a recombinant humanized IgG1 monoclonal antibody, which targets and binds free IgE and prevents it from interacting with Fc ϵ RI and

From the ¹2nd Respiratory Medicine Department, National and Kapodistrian University of Athens, 2nd Respiratory Medicine Department, "Attikon" University Hospital, Chaidari, Athens, Greece; ²Prof, Respiratory Medicine Department, Aristotle University of Thessaloniki, G Papanikolaou Hospital, Thessaloniki, Greece; ³7th Respiratory Medicine Department, Sotiria Hospital, Athens, Greece; ⁴Pulmonologist-Chania, Crete, Greece; ⁵National and Kapodistrian University of Athens National and Kapodistrian University of Athens, 1st Respiratory Medicine Department, "Sotiria" Hospital, Athens, Greece

A. Papaioannou has received advisory board and speakers' fees from Novartis, K. Porpodis has received advisory board and speakers' fees from Novartis, K. Samitas has received speakers' fees from Novartis, E. Zervas has received advisory board and speakers' fees from Novartis, P. Bakakos has received advisory board and speakers' fees from Novartis, M. Gaga has received advisory board and speakers' fees from Novartis, and has received advisory board and speakers' fees from Novartis. The remaining authors have no conflicts of interest pertaining to this article
Abstract presentation, the annual European Respiratory Society (ERS) annual congress meeting 6–9 September, 2020 (virtual congress)

No external funding sources reported

Address correspondence to Andriana I. Papaioannou, M.D., 2nd Respiratory Medicine Department, "Attikon" University Hospital, Chaidari, Athens Greece
E-mail address: papaioannouandriana@gmail.com

Copyright © 2021, OceanSide Publications, Inc., U.S.A.

FcεRII, and, thus, interrupts the IgE-mediated asthma inflammatory cascade at an early stage¹² and reduces both early and late asthma responses.¹³ Omalizumab is indicated as an add-on therapy for patients with uncontrolled persistent severe allergic asthma, and large-scale randomized controlled studies have shown that it is effective in the prevention of exacerbations, symptom improvement, and systemic corticosteroids reduction.^{14–17} Omalizumab has also been shown to be effective in chronic spontaneous urticaria^{18,19} and nasal polyposis²⁰; while efficacy has been also shown in allergic rhinitis.²¹ Because there is more than a decade from its approval as an add-on therapy in severe allergic asthma, several real-life studies have been published and these confirm the results of randomized controlled studies.^{22–26}

The safety of omalizumab has also been established in both randomized controlled trials²⁷ and real-life²⁸ studies, and adverse events suggestive of hypersensitivity reactions (including anaphylaxis, urticaria, and serum sickness) rarely occur and less often are compared with other monoclonal antibodies administered for other indications. Although real-life data provide a great deal of information with regard to the efficacy and safety of omalizumab therapy in severe allergic asthma, to our knowledge, to date, there is no evidence with regard to the optimal duration of such treatment as well as the sustained efficacy and safety of this monoclonal antibody when it is administered for a long time. When taking all these points together, we aimed to determine the sustained effectiveness and safety of long-term treatment with omalizumab in a population in Greece of patients with severe allergic asthma in a real-world setting.

METHODS

Data were collected from four asthma centers in Greece. The patients included in the study were > 18 years old, had a diagnosis of severe uncontrolled allergic asthma, and had received omalizumab based on the physician's assessment.³ To be included in the study, the patients should have been treated with omalizumab for at least 8 years with good adherence to therapy. All the patients were either symptomatic or experienced asthma exacerbations, despite receiving optimal therapy (high-dose inhaled corticosteroids and long-acting β -agonists), with good adherence and good inhaler technique before omalizumab initiation. Furthermore, all the patients had at least one positive skin-prick test or documented *in vitro* reactivity to a perennial aeroallergen (e.g., cat fur, dust mites) and IgE $\geq$ 30 IU/mL. Exclusion criteria were refusal of the patient to participate in the study, nonadherence to treatment, drug interruption for any reason, and pregnancy and lactation.

In all the patients, pulmonary function tests, asthma control (by using the Asthma Control Test [ACT]²⁹), blood eosinophil count, the dose of oral corticosteroids (OCS), and the annual rate of exacerbations were recorded for the year before treatment, for each 6 months during the first year, and annually thereafter. The OCS dose was reduced according to the judgment of the treating physician. Adverse events were also recorded. The study was approved by the ethics committee of "Atticon" Hospital, "Sotiria" Hospital and "Papanikolaou" Hospital, and patients' informed consent was obtained. S. Loukides, M. Gaga, E. Zervas, and S. Papiris designed the study. S. Loukides, P. Bakakos, E. Zervas, K. Samitas, M. Markatos, E. Fouka, K. Porpodis, and D. Papakosta collected the data during baseline and follow up. A.I. Papaioannou, S. Loukides, and P. Bakakos performed the statistical analysis, A.I. Papaioannou, S. Loukides, Myrto Mplizou, and P. Bakakos wrote the main manuscript. All the authors read and approved the final version of the manuscript.

The omalizumab dose and dosing frequency were determined according to baseline total serum IgE level (IU/mL) and body weight (kg) measured before the start of treatment. Omalizumab was administered by subcutaneous injections at a dose determined from the prescribing dosing table.³⁰ Spirometry measurements were performed according to the American Thoracic Society guidelines³¹ and were evaluated by asthma specialists. Asthma exacerbations were defined as events characterized by at least one of the following: (a) worsening of symptoms outside the usual day-to-day variation, (b) increased usage of rescue medication, (c) decline in lung function, (d) use of OCS or intramuscular corticosteroids or an increase in the maintenance dose of OCS for at least 3 consecutive days, and/or (e) urgent or unscheduled visit to the emergency department due to asthma symptoms deterioration.³²

With regard to statistical analysis, categorical variables are presented as number and percentage, and numerical variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile ranges) for normally distributed and skewed data, respectively. Normality of distributions was assessed with the Kolmogorov-Smirnov test. Comparisons of variables between time points were performed by using the Friedman test for repeated measures (for the comparison of data in three or more time points). Statistical significance was established at $p < 0.05$. Data were analyzed by using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL), and graphs were created with Graph Pad Prism 5 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Forty-five patients (66.7% women) with a mean $\pm$ SD age of 55.3 ± 12.2 years were included in the study. The main disease duration was 34.5 ± 16.1 years, and

Table 1 Demographic and functional characteristics of the study patients before omalizumab initiation (N = 45)

Variable	Baseline
Age, mean $\pm$ SD, y	55.3 $\pm$ 12.2
Women, n (%)	30 (66.7)
Current smoker, n (%)	8 (17.8)
No. pack years, mean $\pm$ SD	5.3 $\pm$ 11.5
BMI, mean $\pm$ SD, kg/m ²	28.3 $\pm$ 5.5
Disease duration, mean $\pm$ SD, y	34.5 $\pm$ 16.1
Duration of treatment with omalizumab, mean $\pm$ SD, y	10.6 $\pm$ 1.2
Late onset of asthma, n (%)	22 (48.9)
Allergic rhinitis, n (%)	31 (68.9)
Nasal polyps, n (%)	7 (15.6)
GERD, n (%)	16 (35.6)
OCS use, n (%)	19 (42.2)
OCS dose, mean $\pm$ SD, mg	7.8 $\pm$ 5.7
FEV ₁ , mean $\pm$ SD, % predicted	61.5 $\pm$ 15.7
FEV ₁ , mean $\pm$ SD, L	1.64 $\pm$ 0.52
IgE level, mean $\pm$ SD, IU/L	367.1 $\pm$ 445.5
No. acute exacerbations per year, mean $\pm$ SD	4.1 $\pm$ 1.4
Blood eosinophil count, mean $\pm$ SD, cells/ μ L	278.3 $\pm$ 234.2
ACT score, mean $\pm$ SD	16.2 $\pm$ 2.7

SD = Standard deviation; BMI = body mass index; GERD = gastroesophageal reflux disease; OCS = oral corticosteroid; FEV₁ = forced expiratory volume in 1 second; IgE = immunoglobulin E; ACT = Asthma Control Test.

22 of 45 patients (48.9%) had late-onset asthma. The mean $\pm$ SD duration of treatment with omalizumab was 10.6 $\pm$ 1.2 years. All the patients received treatment with omalizumab for at least 8 years, 42 had data for 9 years, 36 for 10 years, 26 for 11 years, and 9 for 12 years. Nineteen of 45 patients (42.2%) required OCS at baseline due to uncontrolled asthma. Demographic and functional characteristics of the patients at baseline are shown in Table 1.

Nineteen of 45 patients (42.2%) received OCS at baseline. The analysis was performed in the subgroup of patients who received OCS on a daily basis as add-on therapy before omalizumab initiation. The OCS dose was reduced according to the judgment of the treating physician. Four of 19 patients (21.1%) discontinued OCS at 6 months of therapy, whereas, after 4 years of therapy, only approximately half of the patients (47.4%) were still on OCS. Finally, at 8 years of therapy, only six patients (31.6%) were still on OCS. The discontinuation of OCS is shown in Fig. 1A. With regard to OCS reduction, 7 of 19 patients (36.8%) reduced the dose of OCS for $\geq$ 50% after 6 months of

treatment with omalizumab; whereas, after 2 years of therapy, 13 of 19 patients (68.4%) had reduced the daily OCS dose $\geq$ 50%. At the end of the 8th year of treatment, only 3 of 19 patients (21.1%) did not reduce the daily dose of OCS (Fig. 1B). The mean daily OCS dose before omalizumab initiation was 7.8 mg of prednisolone or the equivalent and was reduced to 4.7 mg/day after 6 months of therapy, reaching 1.6 mg/day after 8 years of treatment ($p < 0.001$) (Fig. 1C).

Asthma exacerbations were reduced from 4.1 per year before omalizumab initiation to 1.1 after 1 year of treatment and remained low during all the years up to the 8th year of treatment ($p < 0.001$). The reduction of asthma exacerbations is shown on Fig. 2. Treatment with omalizumab resulted in an improvement in asthma control, expressed as the score in the ACT. The mean value of the ACT score before initiation of treatment was $\sim$ 16.2 and increased to 19.1 after 6 months of treatment, and reached 20.1 after 1 year of omalizumab. The ACT score continued to improve and, after 3 years of treatment, reached a score of 22.1 and remained as high, up to the 8th year of treatment ($p < 0.001$) (Fig. 3A). Treatment with omalizumab was also related to an improvement in the forced expiratory volume in 1 second (% predicted), as shown on Fig. 3, B and C. The mean $\pm$ standard error (SE) number of blood eosinophils before treatment initiation was 238.3 $\pm$ 34.9 cells/ μ L. This mean $\pm$ SE number decreased to 197.6 $\pm$ 20.5 cells/ μ L after 6 months of treatment with omalizumab and reached 160.8 $\pm$ 13.1 cells/ μ L after 8 years of treatment with omalizumab, $p < 0.001$.

ADVERSE EVENTS

During therapy with omalizumab, 11 patients reported local reactions and/or erythema at their injection sites, 8 patients reported upper respiratory tract infection, and 1 patient reported ankle swelling. No severe adverse events were reported during treatment with omalizumab in any patient in our study group.

DISCUSSION

In this study, we showed that the patients with severe allergic asthma who had been treated with omalizumab for at least 8 years showed a long-lasting response, which was characterized by improvements of asthma control and lung function, and reduction of exacerbations. These responses to treatment were observed from the first 6 months of treatment (1 year for the reduction of exacerbations), a further improvement was also observed until the end of the second year of treatment, and all parameters seemed to stabilize thereafter. With regard to the ability to reduce the dose of systemic corticosteroids, a major percentage of patients reduced and even discontinued OCS after the

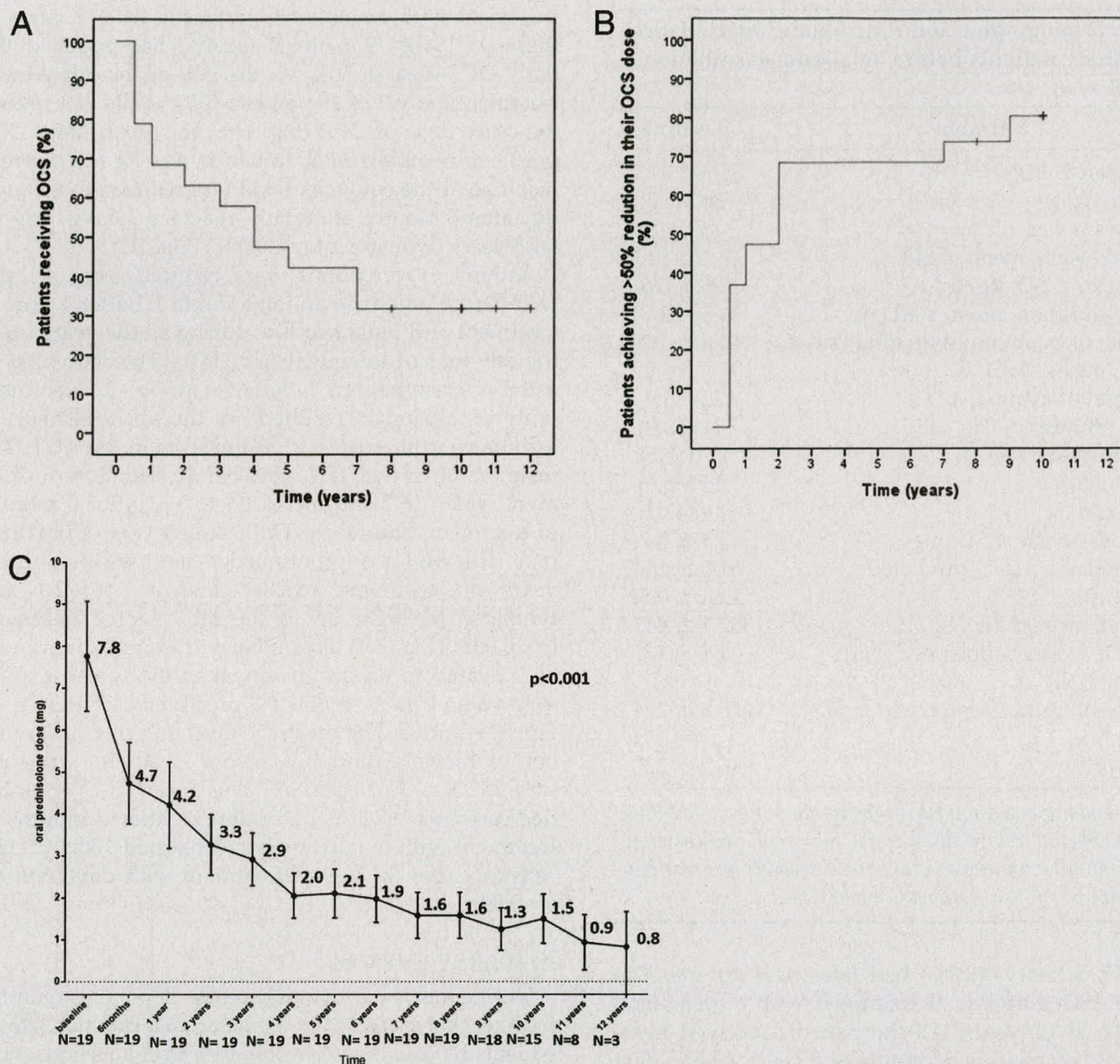


Figure 1. Use of OCS. (A) A Kaplan-Meier curve, showing the percentage of patients discontinuing OCS at every time point. (B) A Kaplan-Meier curve, showing the percentage of the patients who achieved OCS reduction of at least 50% at every time point. (C) The mean daily dose of prednisolone or the equivalent during therapy with omalizumab (mean $\pm$ standard error of the mean). The analysis was performed in the subgroup of patients who received OCS in a daily basis as add-on therapy before omalizumab initiation. The number of patients treated with omalizumab > 8 years is also shown. OCS = Oral corticosteroid.

sixth month of treatment, whereas this percentage became greater in the following years. The aforementioned results showed, not only that omalizumab was an effective therapy for patients with severe allergic asthma, but also that, once achieved, the beneficial effects of this monoclonal antibody were long lasting.

Omalizumab effectiveness in the improvement of asthma control, symptoms, and lung function has been demonstrated in or suggested by several real-world studies.^{22,33–39} In our study, the improvement in asthma control, as suggested by the improvement in the ACT

score, was obvious from the 6th month of treatment, continued to slightly improve until the third year of treatment, and remained stable thereafter. Importantly, the mean ACT score showed an improvement, which was greater than the 3 units known to be the minimally clinically important difference.⁴⁰ Furthermore, the majority of the patients also exceeded the critical score threshold of 20 units, which defines good symptom control at the end of the first year of therapy. Similarly, lung function improved significantly during the first year of therapy, and this improvement was persistent over time, which

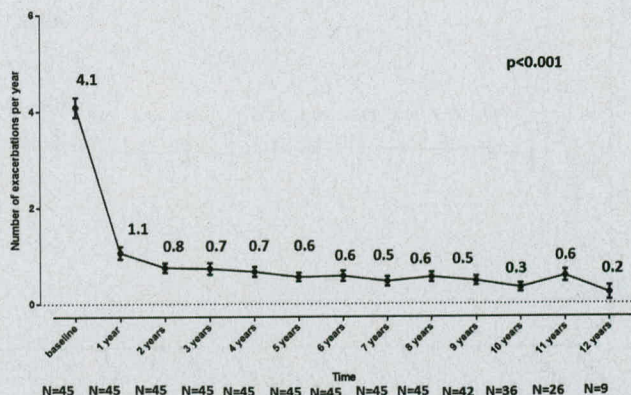


Figure 2. Reduction of asthma exacerbations during treatment with omalizumab. The graph shows the mean $\pm$ standard error (SE). The number of patients treated with omalizumab > 8 years is also shown.

showed again that once the patient responds to therapy, this response remains stable over time.

The steroid sparing effect of biologics is also of great interest because the long-term use of systemic corticosteroids is known to be related to several adverse events, such as hyperglycemia, osteoporosis, cataract, and immunosuppression.⁴¹ Several real-world studies have shown the effectiveness of omalizumab in dose reduction or discontinuation of OCS,^{38,39,42–44} although this has been debated for patients with persistent airway eosinophilia.⁴⁵ In our study, $\sim 20\%$ of the patients discontinued OCS after 1 year of therapy with omalizumab. This was lower compared with other observational studies that showed that $\sim 40\text{--}50\%$ of the patients were able to stop OCS after 12 months of treatment with omalizumab.^{39,44} However, it is important that, in our group of patients, there was an ongoing potential of OCS discontinuation during the following years of treatment, which resulted in a 70% discontinuation after 7 years of therapy.

This observation can be explained by two different facts. First, this was a real-world study in which the treating physician was responsible for making all decisions on treatment alterations according to his or her clinical experience, and, thus, the reduction and/or discontinuation of OCS was not based on a specific predefined protocol. The second fact is the lack of previous clinical experience because omalizumab was the first biologic that became available in everyday clinical practice. The aforementioned conditions, probably resulted in significant concerns on the safety of reducing or discontinuing corticosteroids, especially in patients with severe asthma who had severe asthma and were totally depended on these medications during the previous years. Furthermore, the long-term use of OCS sometimes leads to adrenal insufficiency, and, thus, their total discontinuation is sometimes either difficult or not possible. This, in combination with the observation that 70% of the patients achieved a reduction of $>50\%$ in their OCS dose after 3 years of therapy and that the

mean OCS dose after 3 years of omalizumab therapy was 2.9 mg of prednisolone or the equivalent at the same time point, led to the conclusion that the patients who continued to receive OCS received low doses. Finally, it should be mentioned that reduction of OCS should be performed with caution due to the risk of manifesting Eosinophilic Granulomatosis with Polyangiitis (EGPA), especially in patients with long-term OCS use in which this diagnosis was not carefully ruled out in the first place.⁴⁶ However, in our study, EGPA had been ruled out before omalizumab initiation because all our patients were treated by experienced asthma experts.

In our study, there was a 75% reduction in the annual exacerbation rate from the first years of treatment, which remained during the total period of observation. This reduction in the exacerbation rate was much greater than the 30% reduction described in a meta-analysis of real-life studies³⁸ and from the $\sim 50\%$ reduction observed in some large real-life studies³⁹; however, it was in accordance with other real-life studies.^{33,35,47} A probable explanation for this observation is probably that patients included in this study were all, by definition, responders to omalizumab therapy and that this is the reason why both patients and their physicians have decided not to discontinue therapy for such a long period of time, despite good clinical improvement and asthma control.

Interestingly, we observed a reduction of the total number of blood eosinophils in our patients' group. The ability of omalizumab to reduce eosinophil counts in blood and sputum has been previously reported.^{48,49} Furthermore, a recent study showed that omalizumab resulted in significant reduction of blood eosinophils compared with placebo in adolescents with moderate-to-severe asthma.⁵⁰ This sustained reduction probably contributed to the observed improvements of lung function and the reduction of exacerbations in our group of patients.⁴⁹ However, the possibility that this alteration in the number of blood eosinophils to be related with the aging of our population or in a shift in asthma phenotype could not be excluded.

Our study had several limitations. First, it was a retrospective study and, as stated above, all the participants were good responders by definition. However, according to analysis of our data, we can hypothesize that patients who are carefully selected for omalizumab therapy, present a permanent response, despite long-term treatment. Because there is no evidence to suggest when and how therapy with omalizumab should be discontinued, this decision mainly relied on the patient and the treating physician. The long-term duration of our observational real-life study also offered the opportunity to test and confirm the long-term safety of omalizumab and to conclude that this monoclonal antibody seemed to generally be safe in the long term (>8 years). A second limitation was that, as stated above, the treating

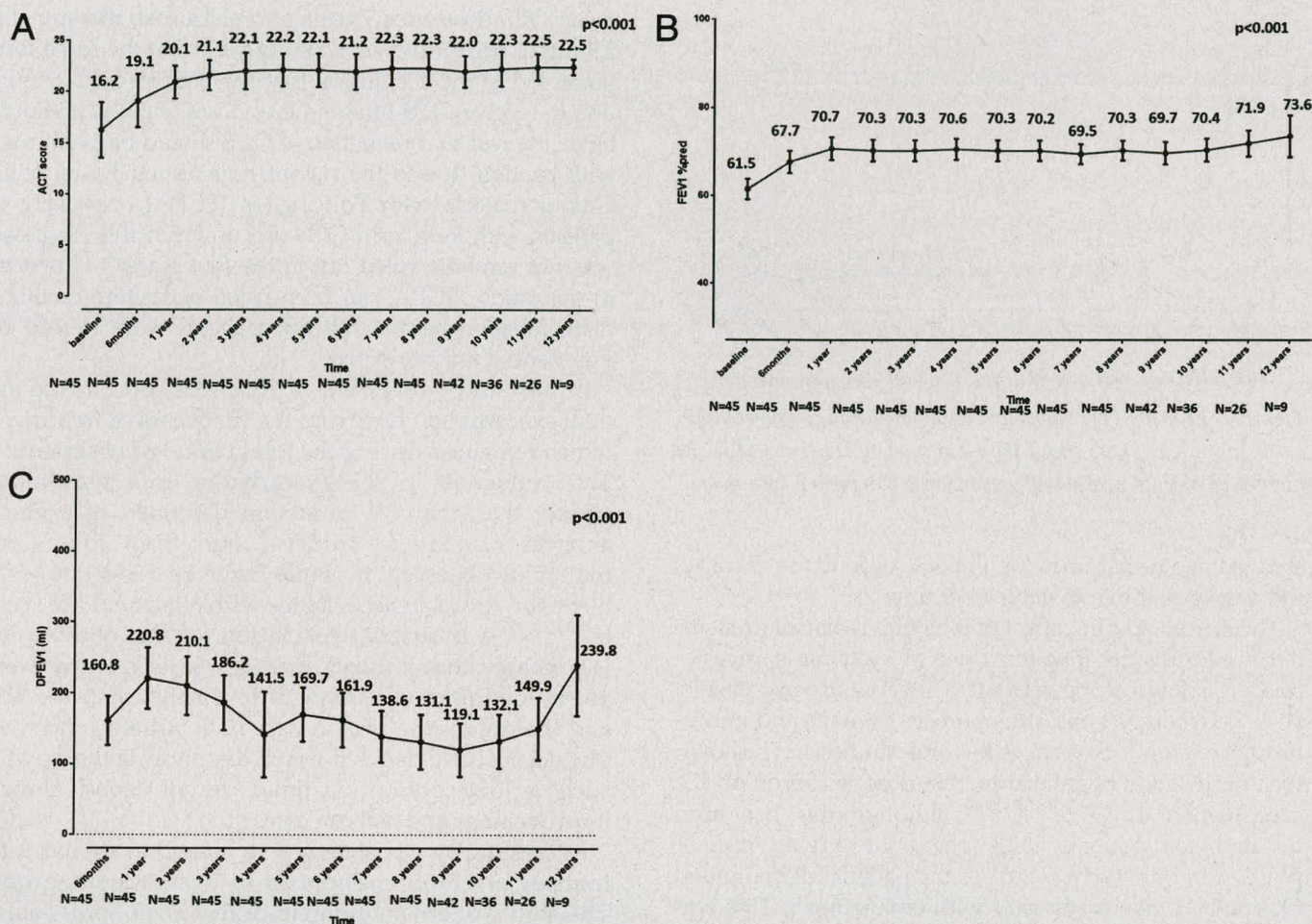


Figure 3. (A) Change in the ACT score, (B) lung function (FEV₁ % pred), and (C) alterations in FEV₁ (mL), after treatment with omalizumab. All the graphs show the mean $\pm$ SE. The number of patients treated with omalizumab > 8 years is also shown. ACT = Asthma Control Test; FEV₁ % pred = forced expiratory volume in 1 second % predicted; SE = standard error.

physician was responsible to make all decisions on treatment alterations, including OCS reduction or discontinuation and these actions were not based on a predefined protocol. This probably resulted in a more prolonged period of time until reduction and/or discontinuation of OCS. However, we believe that the time of OCS reduction and/or discontinuation and the patient characteristics in which this OCS reduction and/or discontinuation should be performed need further investigation and are topics that should probably be addressed in future guidelines for severe asthma treatment.

CONCLUSION

This real-world study showed that, in patients with severe uncontrolled allergic asthma, treatment with omalizumab had a beneficial effect in lung function and asthma control, acted as a steroid-sparing agent, and led to exacerbation reduction. This effectiveness was maintained for a long period of time without severe adverse events, a finding that supported the good safety profile of this monoclonal antibody. The

only question that still remains unanswered is whether these patients with a good response who are treated for a prolonged period of time should or should not attempt discontinuation of this biologic agent.

REFERENCES

- Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010; 181: 315–323.
- To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health.* 2012; 12:204.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014; 43:343–373.
- Cisternas MG, Blanc PD, Yen IH, et al. A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol.* 2003; 111:1212–1218.
- Senna G, Guerriero M, Paggiaro PL, et al. SANI-Severe Asthma Network in Italy: a way forward to monitor severe asthma. *Clin Mol Allergy.* 2017; 15:9.

6. Serra-Batlles J, Plaza V, Morejon E, et al. Costs of asthma according to the degree of severity. *Eur Respir J*. 1998; 12:1322–1326.
7. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J*. 2003; 22:470–477.
8. D'Amato G, Stanziola A, Sanduzzi A, et al. Treating severe allergic asthma with anti-IgE monoclonal antibody (omalizumab): a review. *Multidiscip Respir Med*. 2014; 9:23.
9. Haselkorn T, Borish L, Miller DP, et al. High prevalence of skin test positivity in severe or difficult-to-treat asthma. *J Asthma*. 2006; 43:745–752.
10. Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015; 46:1308–1321.
11. Holgate ST, Djukanovic R, Casale T, et al. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. *Clin Exp Allergy*. 2005; 35:408–416.
12. Presta LG, Lahr SJ, Shields RL, et al. Humanization of an antibody directed against IgE. *J Immunol*. 1993; 151:2623–2632.
13. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med*. 1997; 155:1828–1834.
14. Ayres JG, Higgins B, Chilvers ER, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy*. 2004; 59:701–708.
15. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy*. 2005; 60:302–308.
16. Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004; 34:632–638.
17. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005; 60:309–316.
18. Apalla Z, Sidiropoulos T, Kampouroupoulou E, et al. Real-life, long-term data on efficacy, safety, response and discontinuation patterns of omalizumab in a Greek population with chronic spontaneous urticaria. *Eur J Dermatol*. 2020; 30:716–722.
19. Maurer M, Rosén K, Hsieh H-J, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013; 368:924–935.
20. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020; 146:595–605.
21. Cavaliere C, Begvarfaj E, Incorvaia C, et al. Long-term omalizumab efficacy in allergic rhinitis. *Immunol Lett*. 2020; 227:81–87.
22. Braunstahl G-J, Chen C-W, Maykut R, et al. The eXpReience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. *Respir Med*. 2013; 107:1141–1151.
23. Brusselle G, Michils A, Louis R, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. *Respir Med*. 2009; 103:1633–1642.
24. Deschildre A, Marguet C, Langlois C, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. *Eur Respir J*. 2015; 46:856–859.
25. Di Bona D, Fiorino I, Taurino M, et al. Long-term "real-life" safety of omalizumab in patients with severe uncontrolled asthma: a nine-year study. *Respir Med*. 2017; 130:55–60.
26. Humbert M, Taillé C, Mala L, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J*. 2018; 51:1702523.
27. Corren J, Casale TB, Lanier B, et al. Safety and tolerability of omalizumab. *Clin Exp Allergy*. 2009; 39:788–797.
28. Pelaia C, Calabrese C, Terracciano R, et al. Omalizumab, the first available antibody for biological treatment of severe asthma: more than a decade of real-life effectiveness. *Ther Adv Respir Dis*. 2018; 12:1753466618810192.
29. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004; 113:59–65.
30. https://www.ema.europa.eu/documents/product-information/xolair-epar-product-information_en.pdf
31. Standardization of spirometry, 1994 Update. American Thoracic Society. *Am J Respir Critical Care Med*. 1995; 152:1107–1136.
32. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009; 180:59–99.
33. Korn S, Thielen A, Seyfried S, et al. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med*. 2009; 103:1725–1731.
34. Lopez Tiro JJ, Contreras EA, Ramirez del Pozo ME, et al. Real life study of three years omalizumab in patients with difficult-to-control asthma. *Allergol Immunopathol (Madr)*. 2015; 43:120–126.
35. Schumann C, Kropf C, Wibmer T, et al. Omalizumab in patients with severe asthma: the XCLUSIVE study. *Clin Respir J*. 2012; 6:215–227.
36. Tzortzaki EG, Georgiou A, Kampas D, et al. Long-term omalizumab treatment in severe allergic asthma: the South-Eastern Mediterranean "real-life" experience. *Pulm Pharmacol Ther*. 2012; 25:77–82.
37. Vieira T, de Oliveira JF, da Graça Castel-Branco M. Short and long-term quality of life and asthma control with omalizumab therapy in a real life setting in Portugal. *Allergol Immunopathol (Madr)*. 2014; 42:3–10.
38. Alhossan A, Lee CS, MacDonald K, et al. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: meta-analysis. *J Allergy Clin Immunol Pract*. 2017; 5:1362–1370.e2.
39. Barnes N, Menzies-Gow A, Mansur AH, et al. Effectiveness of omalizumab in severe allergic asthma: a retrospective UK real-world study. *J Asthma*. 2013; 50:529–536.
40. Schatz M, Kosinski M, Yaras AS, et al. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol*. 2009; 124:719–723.e1.
41. Volmer T, Effenberger T, Trautner C, et al. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J*. 2018; 52:1800703.
42. Brodli M, McKean MC, Moss S, et al. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. *Arch Dis Child*. 2012; 97:604–609.
43. Domingo C, Moreno A, Jose Amengual M, et al. Omalizumab in the management of oral corticosteroid-dependent IGE-mediated asthma patients. *Curr Med Res Opin*. 2011; 27:45–53.
44. Braunstahl G-J, Chlumsky J, Peachey G, et al. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic

- asthma in the real-world setting. *Allergy Asthma Clin Immunol.* 2013; 9:47.
45. Mukherjee M, Kjarsgaard M, Radford K, et al. Omalizumab in patients with severe asthma and persistent sputum eosinophilia. *Allergy Asthma Clin Immunol.* 2019; 15:21.
 46. Basta F, Mazzuca C, Nucera E, et al. Omalizumab in eosinophilic granulomatosis with polyangiitis: friend or foe? A systematic literature review. *Clin Exp Rheumatol.* 2020; 38 (suppl 124):214–220.
 47. Molimard M, de Blay F, Didier A, et al. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respir Med.* 2008; 102:71–76.
 48. Massanari M, Holgate ST, Busse WW, et al. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. *Respir Med.* 2010; 104:188–196.
 49. Skiepkowski R, Zieñkowski Z, Łukaszuk M, et al. Changes in blood eosinophilia during omalizumab therapy as a predictor of asthma exacerbation. *Postepy Dermatol Alergol.* 2014; 5:305–309.
 50. Busse WW, Humbert M, Haselkorn T, et al. Effect of omalizumab on lung function and eosinophil levels in adolescents with moderate-to-severe allergic asthma. *Ann Allergy Asthma Immunol.* 2020; 124:190–196. □

Erratum

Erratum: Zhou et al., “Analysis of the long-term efficacy and safety of subcutaneous immunotherapy for atopic dermatitis”

In the article, “Analysis of the long-term efficacy and safety of subcutaneous immunotherapy for atopic dermatitis”: by Jie Zhou, B.S., Shuguang Chen, B.S., and Zhiqiang Song, M.D., Ph.D. J. Zhou and S. Chen contributed equally to this article. J. Zhou and S. Chen conceived and designed the study, S. Chen performed the clinical treatment and collected the data, J. Zhou performed the statistical analysis and wrote the manuscript, and Z. Song supervised the study and critically revised the manuscript. This article appeared in *Allergy Asthma Proc* 42:e47–e54, 2021; doi: 10.2500/aap.2021.42.200126

The online version has been updated.

DOI 10.2500/aap.2021.42.200126

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.