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Real-life Efficacy of Omalizumab After 9 Years of Follow-up

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Omalizumab is frequently used as add-on treatment to inhaled corticosteroids (ICS) and long-acting β2-agonists in patients with suboptimal control of severe asthma. Patients with severe asthma will typically require chronic treatment, although due to the limited amount of data available there are still some concerns about the safety and efficacy of long-term therapy with omalizumab. Herein, in an extension of a previous 4-year study, we report disease-related outcomes of 8 patients with severe persistent allergic asthma who have been followed for a total of 9 years in a real-life setting. Both quality of life (QoL) (evaluated using the Juniper Asthma-Related QoL Questionnaire [AQLQ]) and forced expiratory volume in 1 second (FEV1) showed sustained improvement at 9 years. The median values of AQLQ and FEV1 at 4 years were 5.5 and 82.0% compared to 5.9 and 85.5%, respectively, at 9 years, which were all significantly increased from baseline. After 9 years, the mean annual number of severe exacerbations was 0.63 compared to 5 at baseline. There also appeared to be a trend toward use of a lower dose of ICS at longer follow-up times. After 9 years, there were no safety concerns for continued use of omalizumab, and no asthma-related hospitalizations or emergency department visits were documented over the last 5 years. The present analysis is the longest reported clinical follow-up of omalizumab. Long-term maintenance treatment with omalizumab for up to 9 years is associated with continued benefits in reducing symptoms, exacerbations, and medication burden without any safety concerns.

Key Words: Allergic allergy; omalizumab; chronic; therapy

INTRODUCTION

Severe asthma affects about 10% of all patients with asthma and is associated with high-risk of asthma-related hospitalization, substantial morbidity, high utilization of healthcare resources, and negative impact on the quality of life (QoL).[1] Generally, long-term management is focused on controlling the clinical aspects of the disease.[2] However, while guidelines are available for evaluation, classification, and management, most patients with severe asthma have suboptimal control.[3,4] In fact, adequate disease control is often not achieved despite optimized multidrug therapy with inhaled corticosteroids (ICS) and bronchodilators, which may be related to the existence of different phenotypes.[5]

Omalizumab is a recombinant humanized monoclonal anti-immunoglobulin E (IgE) antibody that inhibits binding of IgE to high-affinity receptors and is used as add-on treatment to ICS and long-acting β2-agonists (LABA) in patients with suboptimal control of severe asthma.[6] Its efficacy has been demonstrated in both phase III trials[7] and by meta-analysis.[8] Abraham *et al.*[9] recently performed a systematic review and meta-analysis of 'real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma, concluding that those showing a positive initial response are likely to show sustained treatment response and benefit considering outcomes related to clinical symptoms, QoL, and utilization of healthcare resources. Another similar study by Lai *et al.*[10] reported that while omalizumab is associated with higher costs than conventional therapies, it nonetheless appears to be cost-effective in patients with severe allergic asthma.

Since patients with severe asthma will require chronic therapy, the efficacy and safety of omalizumab in the long term remain a concern for many. While several investigations have examined the efficacy and safety of omalizumab, most studies have been limited to a relatively short period of time (*i.e.* <1 year), with the exceptions of Tzortzaki *et al.*[11] (4 years), Zazzali

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et al.[12] (5 years), Pace *et al.*[13] (7 years), and our group[14] (4 years). While these studies have generally reported favorable outcomes, longer-term data on the use of omalizumab in severe asthma is clearly lacking. In an extension of our previous 4-year study in 11 patients with severe persistent allergic asthma who were initially enrolled in an international multicenter clinical trial, we have continued to follow 8 of those patients.[14] We herein present disease-related outcomes in these 8 patients after 9 years of follow-up in a real-life setting.

MATERIALS AND METHODS

Study design

This retrospective, observational study was an extension of a previous study in patients with severe allergic asthma and treated with omalizumab. The study design has previously been described.[14] This study was approved by the local ethics committee (protocol number 2011/0006211/03-01-2011). Briefly, the primary objective was to evaluate the persistency of the response to treatment with omalizumab administered as add-on therapy to optimized asthma therapy (using a step-down strategy), in patients with inadequate asthma control, despite treatment according to step IV of Global Initiative for Asthma (GINA) 2002.[15] Safety and tolerability were also monitored.

Evaluation of efficacy

Evaluation of QoL was performed using the Juniper Asthma-Related QoL Questionnaire (AQLQ).[16] The AQLQ is composed of 32 questions which cover 4 domains: activity limitation, symptoms, environmental stimuli, and emotional function. An overall summary index was used, which is the mean of the responses to the 32 items (total score). Serious and mild exacerbations were documented throughout the study period. Serious exacerbations were classified as those requiring systemic steroids, hospitalization, or visits to the emergency department. Mild to moderate exacerbations of asthma were classified as those which required treatment at home or in the physician's office. Lung function was evaluated by measurement of initial forced expiratory volume in 1 second (FEV1).

RESULTS

Mean age of the 8 patients at enrolment was 43±9 years, and 5 were males; the median total IgE level at baseline was 201.58±104.19 IU/mL (range: 68.07 to 364.20 IU/mL). Specific IgE at baseline in the 8 patients included 5 patients with dust mites; 1 with *Alternaria* and dog; 1 with grasses, lanciuola, Betulaceae, cupressacee, *Alternaria*, dog, cat, and mites; and 1 with grasses, composite, Betulaceae, dust mites, cat, and dog. At baseline, all patients were treated with high doses of ICS (beclomethasone dipropionate [BDP] or equivalent)[17] and with regular LABAs (taken separately or as a fixed dose combination); the mean dose of ICS was 1,125±353 μg/day.

Figure shows the changes in AQLQ and FEV1 at baseline, 32 weeks, and 4 and 9 years. Both AQLQ and FEV1 showed improvement at 4 and 9 years, demonstrating the continued efficacy of omalizumab in the very long term. The median values of AQLQ and FEV1 at 4 years were 5.5 and 82.0%, respectively, compared to 5.9 and 85.5%, respectively, at 9 years, which were all significantly increased from baseline. Moreover, after 9 years, the mean annual number of severe exacerbations was 0.63 compared to 5 at baseline. Considering mild+moderate exacerbations, the mean annual number at 9 years was 0.88.

At last follow-up, 7 patients continued to use LABAs and all were given ICS (1 high dose, 2 medium doses, and 5 low doses). At 32 weeks, there were 2 and 6 patients on high and medium dose ICS, respectively, compared to 2 and 5 patients at 4 years. Thus, there appeared to be a trend toward the use of lower dose ICS at longer follow-up times and this is also reflected in the step-down approach used for other control medications, and in

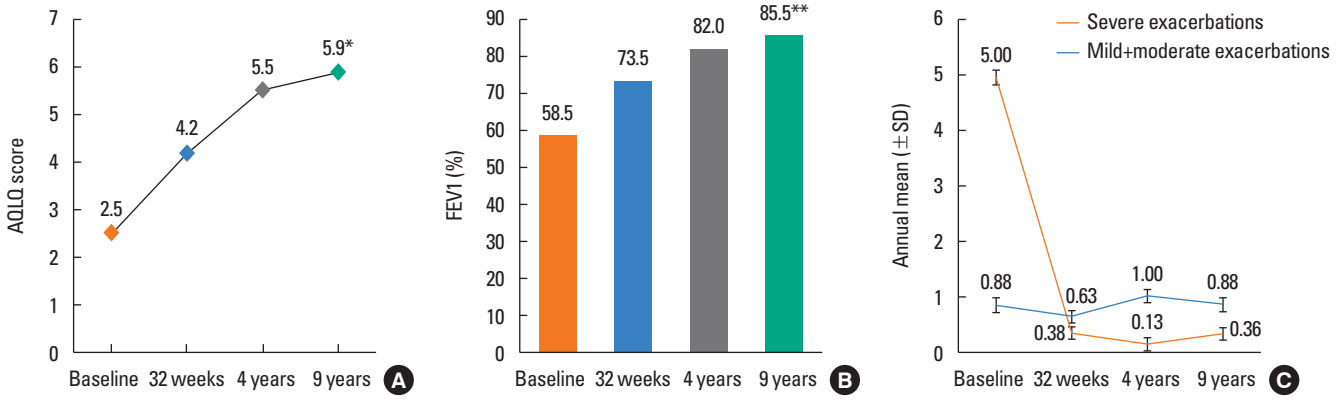

Figure. Improvement in AQLQ score (A), FEV1 (B), and severe and mild+moderate asthma exacerbation rates (C) at baseline, 32 weeks, and 4 and 9 years of omalizumab treatment. AQLQ, Juniper Asthma-Related QoL Questionnaire; FEV1, forced expiratory volume in 1 second; QoL, quality of life. *P<0.001 vs baseline; †P=0.006 vs baseline.

Table. Changes in ICS doses, LABAs, and other medications at baseline, 32 weeks, and 4 and 9 years

Asthma therapy	Baseline	32 wk	4 yr	9 yr
ICS dose				
High dose*	8	2	2	1
Medium dose†	0	6	5	2
Low dose‡	0	0	1	5
LABAs	8	8	8	7
Oral corticosteroids	7	1	0	1
Anti-leukotrienes	4	1	0	2
LAMAs	5	2	2	2
Theophylline	1	0	0	0
SABAs	8	7	3	2

Estimated equipotent daily doses of ICS.17
ICS, inhaled corticosteroids; LAMAs, long-acting muscarinic receptor antagonists; SABAs, short-acting beta-agonists; BDP, beclomethasone dipropionate.
*High dose (μg): BDP >1,000; budesonide >1,000; fluticasone propionate >500 ; †Medium dose (μg): BDP 500-1,000; budesonide 600-1,000; fluticasone propionate >250-500; ‡Low dose (μg): BDP 200-500; budesonide 200-600; fluticasone propionate 100-250.

particular for corticosteroids and anti-leukotrienes at 9 years (Table).

After 9 years, there were no safety concerns for continued use of omalizumab. There were no changes in blood count, creatinine, or liver function parameters. No patient showed any systemic or local side effects related to omalizumab treatment over the entire follow-up period. In addition, no asthma-related hospitalizations or emergency department visits were documented over the last 5 years.

DISCUSSION

Severe persistent asthma remains poorly understood and is problematic to manage from a clinical standpoint. While numerous studies have demonstrated that omalizumab is an effective treatment option for moderate to severe allergic asthma, evidence for its efficacy and safety in the long term remains somewhat limited. In a recent systematic review and meta-analysis, Lai *et al.*[10] reported that treatment with omalizumab for at least 52 weeks was effective and associated with an acceptable safety profile in patients with persistent uncontrolled allergic asthma. Additionally, omalizumab was associated with greater costs than conventional therapy, but was nonetheless considered to be cost-effective if used in patients with severe allergic asthma. The systematic review of Abraham *et al.*[9] came to similar conclusions. These authors found that the benefits of omalizumab may extend up to 2-4 years, and that the drug has both short- and long-term safety profiles that are analogous to those observed in randomized clinical trials. However, the limitations of these analyses are that patients with severe asthma will require chronic therapy and that data are lacking regarding the efficacy and safety of omalizumab over the long term.

To address this issue, we have continued to follow a cohort of 8 patients with severe allergic asthma undergoing treatment with omalizumab. Albeit in this cohort of patients, the present study provides evidence for the continued efficacy of omalizumab in the very long term in treatment of severe persistent allergic asthma. Evaluation of QoL using the AQLQ showed a clear increase even at 32 weeks, with further improvement at 4 years that was maintained at 9 years, at which time the majority of patients still presented a significant increase over baseline values. It can be expected that patients who experience better QoL are more engaged in their care and may show better adherence to medication and lifestyle changes. In addition, spirometry values also showed continued improvement that was maintained throughout 9 years of follow-up. The finding that the effectiveness remains stable over time is further supported by the absence of hospital admissions. The analysis by Abraham *et al.*[9] concluded that patients most likely to benefit from omalizumab include those with significantly impaired lung function who experience varying degrees of symptoms, are at risk of exacerbation that may require corticosteroid therapy, report a significant impairment in QoL, and on ICS therapy. Improved QoL with omalizumab was also confirmed in a recent 24-week study in 616 Chinese patients with moderate-to-severe persistent allergic asthma where significant improvement was seen in AQLQ and ACQ scores.[18] These patient profiles are broadly in line with the present cohort, which may suggest that such patients can also benefit from chronic administration of omalizumab. Our data also extend the results of the Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) study, which showed that omalizumab provides benefits for up to 5 years.[12] In that study in patients ≥12 years old with moderate-to-severe persistent allergic asthma, the percentage of patients treated with omalizumab and with well-controlled asthma (Asthma Control Test score >20) increased from 45% at baseline to 61% at 5 years. For new- starter patients receiving omalizumab, the percentage with well-controlled asthma increased from 25% at baseline to 60% at 5 years. Moreover, patients in the omalizumab-treated cohort experienced reductions in asthma-related work, school, and activity impairment independent of the severity of asthma. The study by Pace *et al.*[13] reported on the effects of omalizumab on asthma outcomes in 7 patients with severe allergic asthmatic patients who were treated for 7 years with add-on omalizumab. In that study, omalizumab was considered to be well tolerated by all patients and associated with improvements in FEV1 and FEV1/forced vital capacity (FVC) ratio, symptom score, asthma exacerbations, and use of antibiotics, nebulized steroids, bronchodilators, and oral corticosteroids that were still apparent after 4 years of treatment and even more pronounced after 7 years of treatment. Those results are also in agreement with our observation that there appeared to

be a trend toward use of a lower dose of ICS at prolonged follow-up times.

One definite limitation of the present study is related to the small number of patients followed, who were initially selected on the basis of restrictive criteria in a clinical trial setting, including origin and ethnicity, who are all Caucasian of Italian origin and were treated at a single center. While such factors may certainly represent bias to be taken into consideration when interpreting these results, they nonetheless show the sustained clinical efficacy of omalizumab in this group of patients in the very long term. This latter aspect is important, especially considering that there is no cure for asthma. As such, treatment is normally focused on controlling the clinical aspects of the disease. Our future prospects are to compare the efficacy of omalizumab in this highly selected population with a group of asthma patients enrolled with wider selection criteria in a post-marketing setting.

The use of omalizumab in patients with severe asthma has been examined in several effectiveness studies in real-life settings. Undoubtedly, such investigations are needed to complement the information from randomized clinical trials to better understand how these findings translate into routine daily practice. This aspect is important considering the heterogeneity of patients and clinical settings. The majority of studies in real-life settings have confirmed that omalizumab treatment significantly improves both objective and subjective parameters of lung function and markedly improves control of asthma in patients with severe allergic asthma. Improved control of asthma is also associated with a reduction in severe exacerbations in the long term as well as a reduced need for systemic corticosteroids and other medications, as shown in the present cohort.

Together with the present data, this would appear to provide further confirmation that omalizumab therapy has a favorable therapeutic impact on the full spectrum of the burden of disease, including symptoms, exacerbations, healthcare utilization, and QoL. Future studies should further address its cost-effectiveness in real-life settings over the long term, which could potentially demonstrate the value associated with omalizumab in severe asthma treatment. To our knowledge, the present analysis is the longest reported clinical follow-up of omalizumab. Notwithstanding its limitations, it confirms that long-term maintenance treatment with omalizumab for at least 9 years is associated with continued benefits for patients in terms of reducing symptoms, exacerbations, and medication burden.

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