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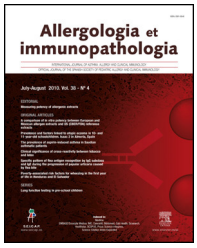

ORIGINAL ARTICLE

Short and long-term quality of life and asthma control with omalizumab therapy in a real life setting in Portugal

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Abstract
Background: The impact of severe asthma on patients' quality of life (QoL) has been previously demonstrated, as well the difficulties in controlling the disease. We aimed to evaluate the effect of omalizumab on QoL and asthma control, and its safety and tolerability in real-life conditions in Portugal.
Methods: Prospective and open-label study in 15 adult patients with uncontrolled severe persistent allergic asthma on omalizumab treatment ≥16 weeks (w). The short (at 16 w) and long-term (at 1 and 2 years) (y) effects of omalizumab were assessed through the Asthma Life Questionnaire (ALQ) and the Asthma Control Test (ACT). Other secondary outcomes were evaluated.
Results: A significant reduction in ALQ total score (at 16 w, $p = 0.002$; at 1 y, $p = 0.033$ and at 2 y, $p = 0.024$), as well as in the 'non-scheduled medical visits' and the 'medication use' domains in both the short and long terms was observed. Regarding ACT, we verified a significant improvement in total score (at 16 w, $p = 0.004$; at 1 y, $p = 0.004$ and at 2 y, $p = 0.008$) and in almost all of the five individual questions. Asthma exacerbations and unscheduled health care visits were significantly decreased. There was a significant rise in lung function and a decrease in daily inhaled steroids dose. The most frequent adverse effects were headaches and nausea.
Conclusions: Omalizumab promoted a global benefit on QoL and asthma control outcomes. It also yielded a reduction in asthma exacerbations and unscheduled health care visits, a steroid-sparing effect, and an improvement in lung function. The drug was found to be generally safe and well-tolerated.

Introduction

Asthma is a chronic inflammatory airways disease and a global disorder which affects about 10% of the worldwide population, and can result in significant morbidity and mortality.[1] The most common asthma phenotype in children is allergic asthma, making up 80–90% of cases,[2] and in adults

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it may exceed 50%.[3] According to the 2002 Global Initiative for Asthma (GINA) classification,[4] about 30% of asthmatic subjects are affected by moderate-to-severe asthma.

The negative impact of moderate-to-severe asthma on patients' quality of life (QoL) and the increased utilisation of health resources resulting from the difficulties in controlling the disease have already been demonstrated.[5,6] To prove such undesirable consequences, there are a great number of questionnaires designed to evaluate asthma-related QoL and control outcomes in clinical trials.

IgE plays a central role in the pathogenesis of allergic asthma.[7] Omalizumab is a recombinant humanized monoclonal antibody that selectively binds to free human IgE preventing it from binding to inflammatory cells, thereby inhibiting allergen-induced activation and subsequent asthma symptoms. Its inclusion in asthma management guidelines has provided expert support for its role in the most serious asthmatic patients with refractory response to high doses of inhaled steroids (IS) and long acting β_2-agonists (LABA) and/or those suffering from systemic steroid dependence.[8,9] Omalizumab was approved in 2003 by the United States (US) Food and Drug Administration (FDA) for the treatment of uncontrolled moderate-to-severe allergic asthma in patients 12 years of age or older. In the European Union (EU), it was approved by the European Medicines Agency (EMA) for uncontrolled severe allergic asthma in 2005 and, since 2009, for children 6–11 years of age.

The state of the art already permits us to identify the clinical benefits of omalizumab as an add-on therapy in patients with uncontrolled moderate-to-severe allergic asthma, with no major adverse effects. Treated patients experience a reduction of symptoms and exacerbations of the condition. A reduction in the usage of preventive and rescue medication, as well as in unscheduled medical visits and hospitalizations also occurs.[10–12] Other assessments verified significant improvements in asthma-related QoL when compared with placebo-treated patients.[13–15] Recent published reports have also documented the real-life effectiveness of omalizumab in Europe.[16–19] Consequently, omalizumab represents an important addition to the current standard treatments for severe IgE-mediated asthma. We aimed to evaluate the effect of omalizumab on QoL and asthma control in a real-life setting, following the introduction of the drug onto the Portuguese market. Safety and tolerability were also assessed.

Materials and methods

Study design

We performed a prospective, open-label and observational study in the first group of intent-to-treat patients, with uncontrolled severe persistent allergic asthma, who received omalizumab treatment in a central hospital in Porto, Portugal.

The primary objectives were to determine, via questionnaires, the short (at 16-week) and long term (at 1 and 2 years) effects of omalizumab as an add-on therapy in QoL and asthma control. As secondary objectives we assessed other indicators, such as exacerbations, unscheduled healthcare utilisation resources, steroids use, lung function, bronchial inflammation, body weight and adverse effects.

During the patients' baseline assessment, the following statistics were collected historically via review of medical files and a clinical interview: the demographic data, duration of asthma-related treatments allergic asthma, asthma-related treatments, asthma symptoms, number of exacerbations, unscheduled healthcare visits, concomitant diseases, lung function tests and patient questionnaire scores regarding the one-year period prior to starting omalizumab.

Almost all of the subsequent medical visits coincided with visits to the hospital required for the drug administration, that is, monthly or bi-weekly, and as such integrated into routine clinical practice.

QoL and asthma control were assessed using the Asthma Life Questionnaire (ALQ) and the Asthma Control Test (ACT), respectively. ALQ was completed at baseline, 16 weeks and every four months. ACT was completed at baseline and monthly or bi-weekly, coinciding with scheduled medical visits. The total scores and domains were compared at short and long terms, and resulted from a weighted average of all the questionnaires in the meantime.

Secondary efficacy variables included the annual number of clinically significant asthma exacerbations, defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids or a doubling of the inhaled steroids dose, in addition to unscheduled healthcare utilisation resources (including general practitioner visits, specialist visits, emergency room visits and hospitalizations).

Spirometry (JAEGER, Viasys Healthcare GmbH, Germany) and exhaled nitric oxide fraction (FeNO) (NIOX®, version 2.0, Aerocrine AB, Sweden) were performed when available at each visit and were compared in the short and long-term.

In addition, we performed a descriptive analysis of all of the above parameters at three years.

Adverse effects were recorded at each visit and blood samples were collected for a haematological assessment, biochemical or other tests, according to medical judgement.

The decision to continue therapy was determined by the treating physician over time, if the patient showed good response and compliance to the treatment.

Patients

The included patients were those for whom the treating physician in his/her best clinical judgement suggested omalizumab, but only after review and agreement of two more medical experts. Adult patients with uncontrolled severe allergic asthma despite treatment with high doses of IS (>1000 μg budesonide/day or equivalent) and LABA, according to the 2006 GINA guidelines followed in the Allergy Department of Hospital de São João, Porto, Portugal, were selected. It was also necessary to demonstrate a perennial allergen sensitization (by skin prick tests and/or specific IgE assay), a reduction in lung function (FEV_1 < 80% of predicted), frequent day or night-time asthma symptoms, multiple exacerbations and the need of systemic steroids, emergency services or hospitalizations during the previous year.

In the period between February 2007 and September 2010, a total of 15 patients started treatment with omalizumab and gave written informed consent prior to initiating this therapy. Approval for the intervention was granted by the Local Ethics Committee.

Medication and dosage

According to the omalizumab criteria prescription approved by the EMA in 2005, patients were required to have an IgE level between 30 and 700 IU/mL and a body weight between 20 and 150 kg, but in three patients the IgE load exceeded the recommended dosing table. Currently, in EU the allowed IgE levels range from 30 to 1500 IU/mL.

The administered dose of omalizumab varied from 75 mg every four weeks to 600 mg every two weeks, based on a chart that considers the patient's IgE level and body weight.[20] Physicians were allowed to prescribe, withdraw or adjust any approved asthma medication in addition to omalizumab, in order to achieve the best control for each patient.

Quality of life and asthma control questionnaires

Subjective asthma-related QoL outcomes were assessed using the ALQ. This questionnaire is a simple self-administered questionnaire comprising 20 questions in a yes/no answer format developed by the American College of Allergy, Asthma and Immunology. It is useful in providing information on asthma diagnosis, control and QoL.[21] ALQ addresses six domains of the impact of asthma on patients' lives: activities and sleep, symptoms, triggers, unscheduled health care use, medication and psychological state. All questions have equal weight and, for each patient, a total ALQ score is calculated as the sum of all positive (yes) responses, ranging from 0 to 20. Lower scores reflect greater QoL impairment. Data from various other publications support the reliability of ALQ in studies of patients with moderate-to-severe asthma. The Portuguese version of the ALQ was previously translated, adapted and validated.[22]

Asthma control was assessed using the ACT. This tool is also a simple self-administered questionnaire comprising five questions which address daily activities, dyspnoea, nocturnal symptoms, rescue medication and self-evaluation of asthma control. Each question has a point scale from 1 to 5, yielding a total score between 5 (poorly controlled asthma) and 25 (well-controlled asthma). An overall ACT score $\leq$19 was found to identify patients with inadequately controlled asthma and a score $\leq$15 predicts uncontrolled asthma.[23] A Portuguese-language version of the ACT was validated.[24]

Statistical methods

For each variable, we used standard methods to calculate proportions, means and standard deviations (SD). The main analysis concerned the changes observed from the short-term (baseline to 16-weeks) to the long-term effect (1 and 2 years) in all the aforementioned statistics. The referred evaluation over the treatment period was made with the Wilcoxon or McNemar non-parametric tests, when appropriate. Safety and tolerability evaluation was made by clinical monitoring of adverse events. The results were considered statistically significant when p-values were <0.05. Data were analysed using IBM SPSS v.19.0 statistical program.

Results

Patients' baseline characteristics

A total of 15 adult patients (13 women, mean age of 46.5 $\pm$ 10.8 years) with uncontrolled severe persistent allergic asthma were selected for omalizumab treatment, and were studied. Fourteen, ten and four patients completed 1, 2 and 3 years of treatment, respectively. Their baseline characteristics are shown in Table 1. All patients had a documented perennial allergen sensitization, most being polysensitized (10 patients, 66.7%). Twelve patients suffered from additional allergic diseases, with allergic rhinitis being the most common. The mean duration of asthma was approximately 36 years.

Mean IgE at baseline was high and ranged widely (mean of 483.5 $\pm$ 473.4 kU/L), while mean body weight was 66.8 $\pm$ 10.6 kg. All patients were treated with high doses of IS (mean of 1653.3 $\pm$ 571.2 μg budesonide/day) and LABA, and two-thirds of the patients were receiving additional controller medications including leukotriene receptor antagonists, anticholinergics or theophylline and derivatives. The majority of patients (53.3%) were also receiving maintenance oral steroids.

Baseline patient questionnaire scores highlighted the poor levels of QoL and asthma control. Mean $\pm$ SD overall scores at baseline for the ALQ and ACT were 15.3 $\pm$ 3.8 points and 12.3 $\pm$ 5.3 points, respectively.

Patients experienced frequent clinically significant asthma exacerbations (mean 7.5 $\pm$ 4.6 exacerbations) and reported on average 6.2 $\pm$ 4.4 unscheduled health care visits due to asthma in the year prior to treatment with omalizumab.

Patients had a mean FEV_1 that was 51.7% of the predicted value; in only two patients, the FEV_1 was > 60% of the prediction. The mean FeNO level was 36.8 $\pm$ 28.8 ppb.

Effect of omalizumab on asthma-related QoL

Total pre-treatment QoL score was low (15.3 points). Across almost all ALQ domains we observed meaningful improvements. We found a significant reduction in ALQ total score (15.3 $\pm$ 3.8 to 11.8 $\pm$ 3.7 points at 16 weeks, p = 0.002; to 12.5 $\pm$ 3.3 points at 1 year, p = 0.033 and 11.8 $\pm$ 4.4 points at 2 years, p = 0.024), and in the 'non-scheduled medical visits' and 'medication use' domains, in both the short and long terms. The 'activities/sleep' domain was only significant at 16 weeks, the 'psychological' domain at 1 year, and the 'symptoms' domain at 16 weeks and 2 years. The 'triggers' domain showed no change over time. The greatest improvement was thus observed in the 'non-scheduled medical visits' and 'medication use' domains (Fig. 1).

Effect of omalizumab on asthma control

Regarding ACT, we verified a significant improvement over time in the total score (12.3 $\pm$ 5.3 to 17.1 $\pm$ 4.6 points at 16

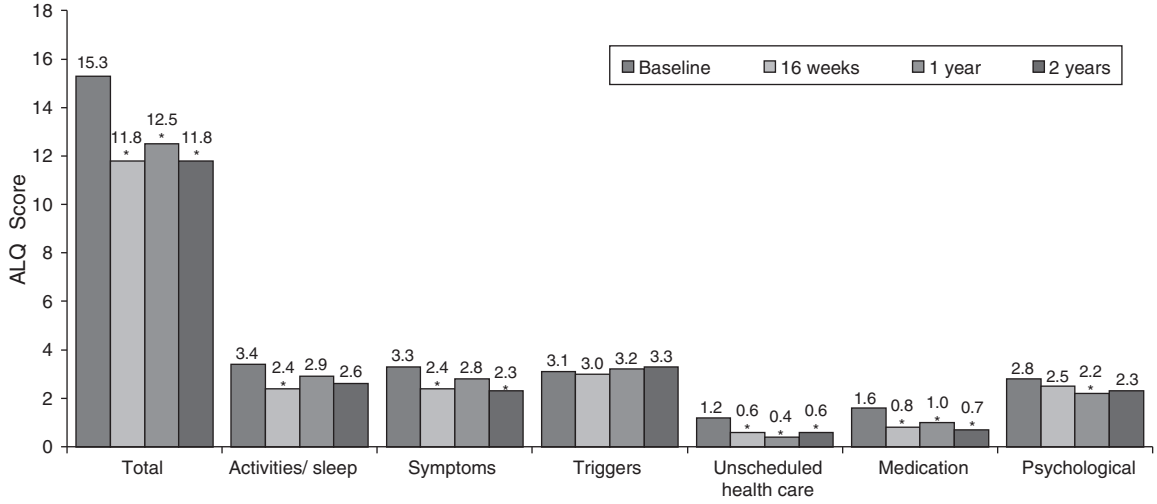

Figure 1 Mean Asthma Life Questionnaire (ALQ) total score and domains during treatment with omalizumab. *$p < 0.05$.

weeks, $p = 0.004$; 17.9 ± 4.3 points at 1 year, $p = 0.004$ and 18.9 ± 4.1 points at 2 years, $p = 0.008$) and in the five individual questions, except for 'asthma self-evaluation control' in the short-term (Fig. 2).

The improvement in asthma control reflected the upgrading in ALQ score conferred by omalizumab therapy.

Secondary outcomes

Upon re-evaluation of patients after one year of treatment, there was a marked reduction of asthma exacerbations and unscheduled health care visits by 70.1% (7.5 ± 4.6 to 2.2 ± 1.5 exacerbations, $p = 0.002$) and 86.1% (6.1 ± 4.4 to 0.9 ± 1.3 visits, $p = 0.002$), respectively. After 2 years, reductions in both parameters remained: 75.9% ($p = 0.05$) in exacerbations and 69.0% ($p = 0.12$) in medical visits.

A significant decrease in the mean daily IS dose (μg budesonide) was also verified (1653.3 ± 571.2 to 1306.7 ± 600.7 at 16 weeks, $p = 0.018$; 1277.0 ± 604.5 at 1 year, $p = 0.011$ and 1111.1 ± 523.4 at 2 years, $p = 0.028$). Fifty-three, 40%, 14% and 10% of patients maintained daily oral steroids use at a basal level, 16 weeks, 1 year and 2 years, respectively.

Concerning lung function, there was a significant rise in FEV_1 (51.7 ± 12.3 to $57.4 \pm 18.2\%$ at 16 weeks, $p = 0.041$; $55.6 \pm 15.7\%$ at 1 year, $p = 0.007$ and $65.0 \pm 12.0\%$ at 2 years, $p = 0.007$).

There were no meaningful variations in FeNO, except in the mean value at 1 year (36.8 ± 28.8 to 20.0 ± 11.2 ppb, $p = 0.23$) or in body weight.

The most frequent adverse effects were headaches and nausea (four cases), and asthenia and paresthesias (two cases). One patient developed a malignant breast

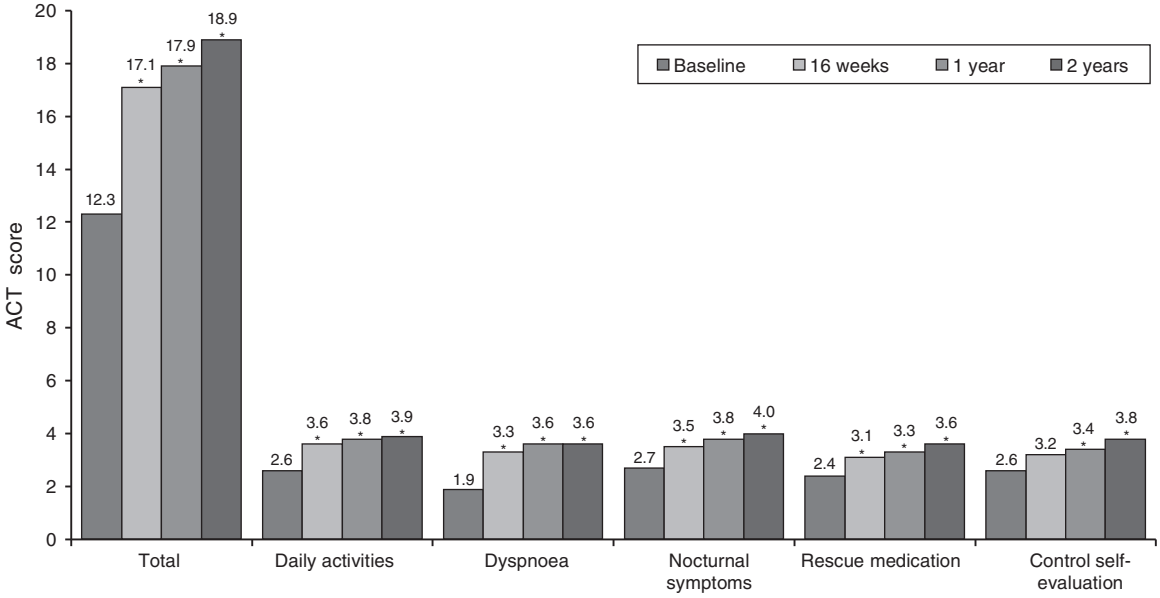

Figure 2 Mean Asthma Control Test (ACT) total score and domains during treatment with omalizumab. *$p < 0.05$.

Table 1 Demographic and baseline clinical characteristics of patients treated with omalizumab.

Baseline characteristics	$N = 15$
Age, mean ± SD (years)	46.5 ± 10.8
Female, *n* (%)	13 (86.7)
Body weight, mean ± SD (Kg)	66.8 ± 10.6
Serum total IgE	
Mean ± SD (KU/L)	483.5 ± 473.4
Minimum–maximum	75.0–1865.0
Smoking history	
Ex-smoker, *n* (%)	1 (6.7)
Never smoked, *n* (%)	14 (93.3)
Duration of asthma, mean ± SD (years)	36.3 ± 10.8
Additional allergic diseases	
Allergic rhinitis/rhinoconjunctivitis, *n* (%)	12 (80.0)
Food allergy	3 (20.0)
Atopic dermatitis	2 (13.3)
Urticaria	2 (13.3)
Aeroallergens sensitisation	
Mites	15 (100.0)
Animal dander	6 (40.0)
Pollens	6 (40.0)
Asthma medication	
Inhaled steroids dose, mean ± SD (μg budesonide/day)	1653.3 ± 571.2
Oral steroids (maintenance), *n* (%)	8 (53.3)
Leukotriene antagonists, *n* (%)	9 (60.0)
Anticholinergics, *n* (%)	4 (26.7)
Theophylline/derivates, *n* (%)	2 (13.3)
FEV_1, mean ± SD (% of predicted)	51.7 ± 12.3
FeNO, mean ± SD (ppb)	36.8 ± 28.3
ALQ score, mean ± SD	15.3 ± 3.8
Activities/sleep	3.4 ± 1.0
Symptoms	3.3 ± 1.2
Triggers	3.1 ± 1.1
Unscheduled health care use	1.2 ± 0.7
Medication	1.6 ± 1.0
Psychological	2.8 ± 0.4
ACT total score, mean ± SD	12.3 ± 5.3
Daily activities	2.6 ± 1.3
Dyspnoea	1.9 ± 1.3
Nocturnal symptoms	2.7 ± 1.5
Rescue medication	2.4 ± 1.2
Control self-evaluation	2.6 ± 1.1
Asthma exacerbations	7.5 ± 4.6
Unscheduled health care visits	6.1 ± 4.4

ACT – Asthma Control Test; ALQ – Asthma Life Questionnaire; FeNO – exhaled nitric oxide fraction; FEV_1 – forced expiratory volume in one second; IgE – immunoglobulin E; SD – standard deviation.

neoplasm after 3.5 years of treatment, although the association of the tumour's development with omalizumab therapy is questionable. Four patients discontinued omalizumab treatment, three due to adverse effects (Table 2) and one for non-compliance to the drug after 2 years. No patient discontinued because of the treatment's ineffectiveness.

From the descriptive analysis at 3 years, we verified a progressive improvement in overall ALQ score (8.3 ± 3.8 points) and the greatest improvement in overall ACT score (20.5 ± 3.8 points); note that only in this stage asthma could be considered ''well controlled'', according to test's interpretation. The annual rates of asthma exacerbations and unscheduled health care visits remained low. The mean dose of IS was 1440.0 ± 649.9 μg budesonide/day. We also verified a constancy on lung function (67.5 ± 7.5% of predicted) and a pronounced reduction in FeNO values (16.0 ± 4.3 ppb). The scattering in the plots and the limited availability of data prevent any firm assumptions about these results from being made, especially about IS dose and FeNO.

Table 2 Adverse effects in patients treated with omalizumab.

Adverse effects	*n* (%)	Discontinuation of treatment, yes/no (time)
Headache	4 (26.7)	No
Nausea	4 (26.7)	No
Myalgia, paresthesias	2 (13.3)	Yes, 1 patient after 3.2 years
Exuberant injection site reactions	2 (13.3)	No
Repeated acute asthma episodes	1 (6.7)	Yes, after 2 years
Breast neoplasm	1 (6.7)	Yes, after 3.5 years

Discussion

Despite guideline-consistent management to treat persistent asthma, many patients maintain symptoms and acute exacerbations frequently, resulting in an inadequate control that significantly affects daily activities, functioning, well-being, and asthma-related QoL. Therefore, improving the health-related QoL and asthma control should be one of the primary goals in asthma management. The most extensive systematic review about omalizumab as an add-on therapy in schoolchildren, adolescents, and adults with moderate-to-severe persistent allergic asthma demonstrated its clinical efficacy and safety.[10] Improvements in QoL were also verified through pooled analysis,[14,15] including in real-life settings.[16–19] This rationale supported our study and summarizes the clinical experience with omalizumab in a cohort of Portuguese patients with uncontrolled severe allergic asthma, following the approval of the drug within the EU and its debut in the Portuguese market. This is the first analysis of the effects of omalizumab in real-life scenarios in our country, outside that of clinical trials.

Our patients were selected according to the clinical criteria recommended by the EMA for the use of omalizumab, except for the three patients with IgE values outside the approved limits, reflecting a sample that was receiving high doses of IS, with poor lung function, and with a high rate of asthma-related events in the year preceding treatment with the drug. It is noteworthy that over half of our patients were on oral maintenance steroids, an exclusion criterion for most of the phase III omalizumab trials.

Omalizumab treatment efficacy is often evaluated at 16 weeks, but in many patients an extension of the treatment is essential to improve symptoms, medication use, lung function and QoL outcomes. For this reason, we extended the evaluation up to 3 years of treatment.

There are no gold standards for measuring QoL and asthma control. Both parameters are complex, as well as the disease. Composite measures, such as questionnaires, are therefore advocated and were used by us.

Our data suggest that omalizumab was associated with important improvements in asthma-related QoL outcomes, especially in non-scheduled medical visits and medication use. Several published studies about QoL with omalizumab therapy demonstrated such significant improvements, but employed the Asthma Quality of Life Questionnaire (AQLQ) instead, which limits comparisons with our results. AQLQ is a tool that consists of 32 questions grouped into four domains (activity limitations, emotions, symptoms and environmental exposure), in which each question is answered by the patient on a 7-point scale, with a score of 1 representing the greatest impairment and a score of 7 representing no impairment during the preceding two weeks. Items were equally weighted and reported as the mean score for each domain.[25] A clinically meaningful improvement in QoL is defined as an increase of $\geq$0.5-point from baseline.[26] The meta-analysis performed by Niebauer et al., showed a 1.6–2.1-fold increase in the proportion of patients achieving a moderate-to-large overall asthma-related QoL effect in the omalizumab-treated group, compared with the placebo-group during the steroid-stabilization and steroid-reduction phases. The largest effects were observed in symptoms and overall scores, suggesting a broad impact on patient functionality and well-being.[14] Chips B et al. performed a pooled analysis of six controlled clinical trials in patients exclusively with severe persistent allergic asthma, which presented significant greater improvements in total AQLQ score when compared to the control group (mean increases of 1.01 and 0.61 points, respectively, $p < 0.001$).[15]

As an add-on to current asthma therapy, omalizumab significantly improved disease control in all domains, although its employment did not achieve levels of 'completely controlled' pathology, according to the test's interpretation. Currently, experts acknowledge that achieving optimal disease control in patients with severe persistent asthma may not be possible.[9] These patients frequently receive other treatments – such as leukotriene antagonists, theophylline and oral steroids, among others – in addition to their primary therapy with IS and LABA, obtaining a slight improvement in the disease's control. Thereby, less limitation in daily activities, fewer episodes of dyspnoea and nocturnal symptoms and less rescue medication are highly relevant and clinically meaningful for patients with severe asthma.

Post-marketing surveillance trials performed in several EU countries confirmed the clinically relevant effect of omalizumab on asthma symptoms and level of asthma control in the majority of allergic patients with severe asthma treated in real-life situations.[19,27] The PERSIST study evaluated 159 patients in a real-life setting in Belgium. After 16 and 52 weeks, physician-rated global evaluation of treatment effectiveness was recorded as 'good' or 'excellent' in 82 and 72% of patients, respectively.[17] In other efficacy studies in France and Germany, 51% of patients who received add-on therapy with omalizumab were able to reduce or stop maintenance oral steroid use.[18] The post-marketing, non-interventional, observational registry (eXpeRience) that aims to collect data on the treatment effectiveness and safety of omalizumab in 'real-world' practice, plans to assess 900 patients in approximately 15 countries (Europe, Canada, South America and Asia).[28] It will be interesting to evaluate their results.

Several studies, either in placebo-controlled trials or in real-life situations, have focused on other parameters such as asthma exacerbations and unscheduled health care visits, showing a significant reduction in both.[10,11] One of the most recent studies conducted by Hanania et al. showed a 25% relative reduction of asthma exacerbations when comparing a placebo with omalizumab during 48 weeks of treatment.[12] The first study in a real-life setting showed that patients with follow-up data at five months or more had experienced 62% fewer exacerbations requiring oral steroids, 65% fewer emergency department visits and 29% fewer hospitalizations.[27] Asthma exacerbations and unscheduled health care visits were also significantly decreased in our patients by 70.1% and 86.1%, respectively, after one year of treatment.

Patients treated with omalizumab were able to significantly reduce their daily IS budesonide use. We also verified a reduction in the number of patients maintaining treatment with oral steroids. A lower consumption of medication is a criterion of effectiveness which is already supported by other studies.[10]

Regarding the effects of omalizumab on lung function, inconsistent data have been reported by various clinical trials, but some yielded increases in predicted FEV_1.[29,30] This observation is consistent with the reported relationship between recurrent asthma exacerbations, typical in patients with severe asthma, and deterioration of lung function, that can be interrupted by omalizumab.[31]

Another interesting query is the effect of omalizumab on FeNO, a marker of bronchial inflammation. The limited available data from our sample curtails our interpretation. A paediatric study carried out in allergic asthmatic children demonstrated that omalizumab was able to maintain the FeNO at significantly lower levels.[32] These findings have also been recently confirmed by another study lasting 48 weeks, which demonstrated that omalizumab reduced FeNO levels compared to the placebo.[12]

We can speculate whether there is an overestimation of the effect of omalizumab, due to a higher treatment adherence rate inherent to regular and filed medical visits. In fact, studies about chronic diseases show poor patient-adherence to medication and, similarly, physician-adherence to guidelines.[33] As such, scheduled visits and close monitoring may favour treatment adherence, with greater clinical benefits.

When to stop omalizumab therapy, and its long-term effects, are questions that yet remain to be answered. Long-standing observational studies suggest that following several years of treatment, the clinical benefits of omalizumab persist even after discontinuation of the drug. Pace et al., in one study involving severe asthmatics on omalizumab, observed improved pulmonary function, reduced symptom scores and asthma exacerbations, reduced use of antibiotics, bronchodilators, IS and oral corticosteroids after maintenance

of seven years of treatment.[34] Nopp et al. in their follow-up studies after omalizumab withdrawal, reported improved or unchanged asthma compared to the period of when drug treatment was ongoing.[35,36]

In our study, six patients experienced at least one adverse event (Table 2) that was consistent with omalizumab's drug information leaflet. Overall, omalizumab is safe and well-tolerated; the most commonly reported adverse events are local injection-site reactions. Other relatively frequent adverse effects include headache, fatigue, and nausea, as per what occurred to our patients.[10] Another large analysis of safety data from clinical trials was published in 2009 and included at least 7500 patients.[37] It showed that omalizumab exhibited a good safety and tolerability profile that was maintained for up to four years (4.2% prevalence of serious adverse effects in the omalizumab group and 3.8% in the placebo group). That review reported a prevalence of anaphylaxis of 0.14% in treated patients and 0.07% in the placebo group. The frequency of adverse effects suggesting hypersensitivity reactions (such as anaphylaxis or urticaria) was also low; Cox L et al. reported a rate of 0.09%.[38]

One of our patients developed a breast neoplasm after 3.5 years of treatment, but causal relation has not been established. At present, there is no evidence that omalizumab is associated with the development of malignancy, although after completion of the Phase III clinical trials in the USA, it was noted that the prevalence of malignancy was higher in patients treated with omalizumab (20 of 4127 patients or 0.5%) versus placebo (5 of 2236 or 0.18%). The most common malignancies were on the skin (non-melanoma), breast and prostate.[39] A careful analysis of all such events did not establish a causal relationship between omalizumab and malignancy.

In 2009, the FDA raised concerns about the cardiovascular and cerebrovascular adverse events (ischaemic heart disease, arrhythmias, cardiac failure, pulmonary hypertension, and thrombotic events) in the omalizumab treatment group of the EXCELS study. Such events were not described in previous analyses of clinical data, and a recent systematic review of eight placebo-controlled trials in 3429 participants has not detected increased cardiovascular risk caused by the use of omalizumab.[10] The FDA is not recommending any changes in the prescription information at this time.

The long-term safety profile of omalizumab remains a concern. The EXCELS study, which started in 2004, is an ongoing observational study that will provide additional data on existing concerns with long-term use of omalizumab (namely anaphylaxis, malignancy and cardiovascular issues).[40]

Our study has some limitations: it was observational and open-label, not a randomised, controlled trial. It was not a population-based study. Thus, patient selection was based on physician-perceived benefit to the patient, which may constitute a bias factor. The results were based on comparisons within the same patient-group instead of making those with a control group. It would be interesting to evaluate the effect of omalizumab in other concomitant IgE-mediated allergic diseases, such as allergic rhinitis, which is highly prevalent in patients with allergic asthma. However, our study was not designed to test these effects.

Conclusions

Patients selected to be treated with omalizumab by their physicians under ''real-life'' conditions, experienced a global benefit on QoL and asthma control outcomes. A reduction in the rate of clinically significant asthma exacerbations and unscheduled health care visits, as well as a steroid-sparing effect and an improvement in lung function were observed. These benefits suggest that omalizumab is an effective intervention as an add-on therapy in the management of severe persistent allergic asthma. Our experience verified that even smaller effect sizes are important to patients and they are pleased with the degree of improvement in their previously poorly-controlled symptoms. Omalizumab was generally safe and well tolerated, however, as with any relatively new class of drugs, constant surveillance is needed as its utilisation in real life practice continues to increase.

Authorship

The authors confirm that the manuscript has not been published elsewhere and is not under consideration for publication elsewhere.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflict of interest

The authors have no conflict of interest to declare.

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