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A study into efficacy of omalizumab therapy in patients with severe persistent allergic asthma at a tertiary referral centre for asthma in Ireland

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Summary

Background: Asthma is a chronic airway disease characterized by airway inflammation, bronchial hyperresponsiveness and airflow obstruction. Patients with persistent symptoms despite maximum standard treatment as per Global Initiative of Asthma guidelines are considered to have severe persistent asthma. Omalizumab is a recombinant humanized monoclonal antibody licenced for use as an add-on therapy in these patients.

Aim: To assess the clinical benefit amongst responders to omalizumab therapy at a tertiary referral centre.

Methods: This was a retrospective audit assessing the effect of omalizumab therapy on asthma control, frequency of exacerbation and hospitalization rates over 6 months before and after therapy.

Results: The study included 30 responders (14 females). There was a reduction in exacerbation and hospitalization rates following initiation of omalizumab, 73 and 91%, respectively (P-value < 0.0001). The number of exacerbations decreased from 3.48 ± 2.20 to 0.93 ± 0.83 and the mean number of admissions decreased from 1.07 ± 1.1 to 0.1 ± 0.40 over the study duration ($P < 0.001$). There was 73% reduction in the weekly need for rescue salbutamol therapy with mean of 30.33 ± 6.49 puffs to 8.23 ± 1.51 puffs after omalizumab therapy ($P < 0.0001$). Seventy-nine per cent of patients were able to reduce their maintenance oral corticosteroid therapy.

Conclusions: Overall, responders to omalizumab therapy are less likely to experience an asthma exacerbation and hospitalization. They were also more likely to reduce maintenance corticosteroid therapy and the need for rescue reliever therapy. These data suggest that omalizumab has proven effective in improving health outcomes for a cohort of carefully selected patients with severe allergic asthma in Ireland.

Introduction

Asthma is a chronic airway disease characterized by airway inflammation, bronchial hyperresponsiveness and airflow obstruction. The interaction of these features determines clinical manifestations, severity and response to treatment. The availability of Global Initiative of Asthma (GINA) guidelines benefits in standardizing practice and improving disease management (2007). Patients with persistent symptoms despite maximum standard treatment as per GINA guidelines are considered to have severe persistent asthma.[1] An exacerbation in these patients is often associated with high morbidity and mortality.[2,3] These exacerbations account for healthcare utility costs including medications, casualty visits and hospitalizations. Omalizumab is a recombinant

humanized monoclonal antibody licenced for use in severe allergic asthma and as an add-on therapy in the stepwise pharmacotherapy approach amongst patients who are poorly controlled with inhaled corticosteroid (ICS) and long-acting β2 agonists (LABA). Many studies have identified that omalizumab is effective in reducing corticosteroids requirements, reliever usage, reduce airway inflammation, exacerbation, hospitalization and improve asthma related quality of life.[2,4,5] The aim of this study is to assess the clinical benefit amongst responders to omalizumab therapy at a tertiary referral centre. We hypothesized that omalizumab therapy reduced the frequency of exacerbations and hospitalization rates.

Methods

A retrospective audit was performed on 51 patients with severe persistent allergic asthma who fulfilled the criteria for omalizumab therapy as per GINA guidelines. Only omalizumab responders were included in the analysis ($n = 30$) based on chart review. Patient demographics included age, gender, duration of asthma and smoking history. Asthma control over 6 months prior to and 6 months after commencement of omalizumab therapy was analysed by taking into account the number of exacerbations and hospitalizations in addition to maintenance of medication dosages, need for rescue reliever therapy, serum immunoglobulin E (IgE) levels and pulmonary function testing. The dose and frequency of omalizumab which they received at 2 to 4 week intervals was based on patient's weight and serum IgE titres. The primary outcomes of the study were exacerbation and hospitalization rates over the outlined study period. An exacerbation was defined as poorly controlled symptoms leading to increase in reliever usage, commencement of steroids or antibiotic therapy, casualty visit or hospitalization. Secondary outcomes looked at the need for weekly rescue salbutamol usage, change in maximum standard treatment and change in pulmonary function before and after initiation of therapy. The statistical analysis used was paired *t*-test. The data for all variables were assumed to be not normally distributed, and a non-parametric Wilcoxon signed-rank test was performed to test the median difference between pre- and post-data. The *P*-value for the median difference between pre- and post-data was tested against the significance level of 0.05. The data were analysed using Graph Pad Prism.

Results

A total of 51 patients were screened, 21 were regarded as non-responders and treatment was discontinued after 4 months of therapy. Of the remaining 30 patients who were all responders, 16 patients (53%) were female. The baseline characteristics of the 30 responders analysed are shown in Table 1. Patients required a mean dose of 1760 mcg/day beclomethasone dipropionate (BDP) equivalent of ICS and LABA therapy initially. Twenty-six of the 30 patients (87%) required other controller medications including leukotriene modifier or xanthine derivatives. Fourteen patients (47%) of the cohort population were on oral corticosteroids as maintenance therapy prior to omalizumab therapy. The total duration that these responders were receiving omalizumab therapy at the time of analysis at the author's institution ranged from 6 to 70 months.

The number of asthma exacerbations and hospitalizations of our patients in the 6 months prior to and 6 months post-omalizumab therapy is shown in Figures 1 and 2. A 73% reduction in the number of exacerbations was noted with the initiation of this add-on therapy. The mean number of exacerbations prior to treatment was 3.48 ± 2.20 and significantly reduced to 0.93 ± 0.83 post-treatment ($P < 0.0001$). In the 6 months prior to omalizumab, 18 of 30 patients (60%) required hospitalization, in contrast to 2 of 30 (6.7%) in the 6 months after. There was a 91% reduction in the mean number of admissions from 1.07 ± 1.1 6 months before to 0.1 ± 0.40 6 months after treatment ($P < 0.001$). The weekly need for rescue salbutamol therapy saw a 73% reduction with mean of 30.33 ± 6.49 puffs in the 6 months before treatment to 8.23 ± 1.51 puffs after treatment ($P < 0.0001$; Figure 3). Ten patients (33%) demonstrated a reduction in dose of ICS maintenance therapy.

Amongst the 14 patients who required maintenance oral corticosteroids beforehand, 50% of them had successfully discontinued after 6 months omalizumab therapy. Four of the patients (29%) had required a reduced dose, whereas only three patients (21%) remained on the same dosing. There was no significant change in pulmonary function of our patients over the study period. FEV1% post-treatment increased by $6.01 \pm 9.98\%$ in keeping with 174 ± 278 ml post-treatment.

Discussion

The findings of this audit identify a clear benefit to the use of omalizumab treatment at a tertiary referral centre for asthma in Ireland. The significant reduction in the number of exacerbations, hospitalizations

Table 1 Baseline characteristics of responders

Total patients screened (*n*)	50
Total non-responders to omalizumab therapy (*n*)	20
Total responders to omalizumab therapy (*n*)	30
Gender (M:F)	14:16
Mean age, years (range)	45.6 (21–75)
Mean duration of asthma, years (range)	13.4 (1–40)
Mean serum total IgE level, IU/ml (range)	259.4 (7–1790)
Smoking history (never:ex:current)	24:6:0
Mean daily ICS dose (mcg/day) BDP equivalent (SD)	1760 ± 851.7
LABA use (*n* = 30)	100%
Other controller medications (*n* = 26)	87%
Maintenance oral corticosteroids (*n* = 14)	47%
Follow-up months on treatment (range)	36.5 (6–70)
FEV1% predicted pre-treatment (SD)	71.17 ± 23.61

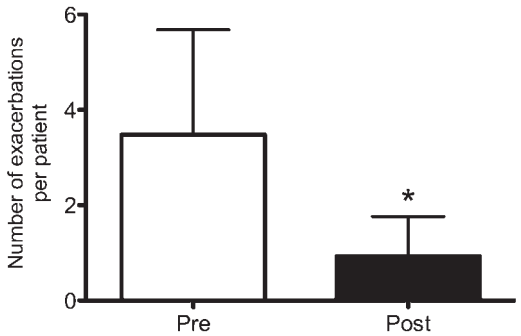

Figure 1. Effect of omalizumab therapy on the mean number of exacerbations per patient in the 6 months before (pre) and 6 months after (post) initiating therapy. Data are mean values ± SD (* denotes $P < 0.0001$).

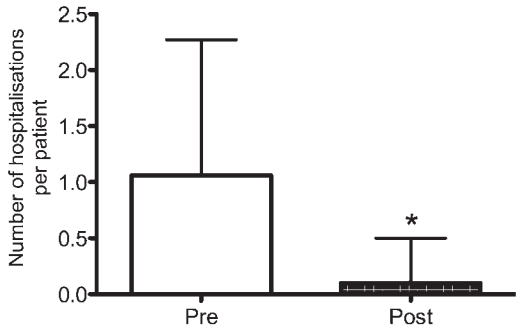

Figure 2. Effect of omalizumab therapy on mean number of hospitalizations per patient in the 6 months before (pre) and 6 months after (post) starting therapy. Data are mean values ± SD (* denotes $P < 0.0001$).

and weekly need for rescue reliever usage validate the clinical benefits of omalizumab therapy in our population. The reduction in inhaled and oral corticosteroid use reflects improved symptom control thereby facilitating step down from maximum standard therapy. Costello *et al*. reported exacerbations rates of the Irish population in the same study duration to be 3.18 ± 2.3 pre-treatment and 1.24 ± 1.5 post-treatment, whilst hospitalizations rates of 2.4 ± 3 pre-treatment fell to 0.8 ± 3 post-treatment, respectively.[5] Our outcomes appear superior and statistically significant when compared with the national sample, which revealed an overall 61% reduction in exacerbation rates and 67% reduction in hospitalizations.

Improved outcomes may be explained through stringent patient selection. Oba and Salzman suggested that omalizumab therapy should be given to poorly controlled asthmatic patients who are non-smokers.[6] The patient cohort identified at our centre did not include any current smokers. Smoking elevates the numbers of pro-inflammatory cells, such as macrophages and neutrophils or goblet cells and enhances release of cytokines.[7,8]

Various healthcare professionals in clinical settings carry out subcutaneous omalizumab administration within Ireland. Therapy may be delivered by a doctor or nursing staff at the outpatient department, infusion unit, day hospital or medical admission units. Omalizumab administration at our local hospital is always performed by a respiratory trained nurse specialist. The brief consultation during administration is used to explore any change in respiratory symptoms and may proceed to a physical examination and further investigations. Specialist nurse support and education at scheduled clinic visits may have a role in enhanced adherence to standard treatment.

A limitation to this study is the absence of a control group. However, many previous placebo controlled trials have demonstrated a positive response from omalizumab therapy.[9–11] Whilst a placebo effect is recognized across studies, omalizumab administration has repeatedly demonstrated a

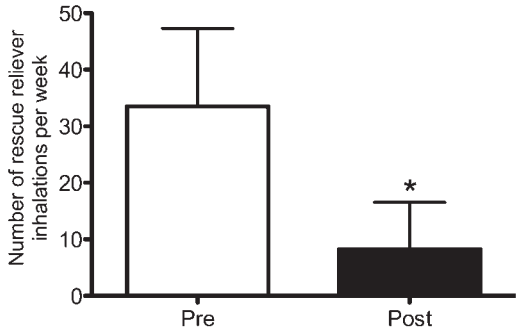

Figure 3. Effect of omalizumab therapy on number of rescue reliever inhalations per week. Data are mean values ± SD (* denotes $P < 0.0001$).

significant reduction in the frequency of exacerbations, need for reliever use and improvement in asthma quality of life scores when compared with placebo therapy.[12,13]

A potential criticism is that only responders after an initial 16-week therapy were included. Those who respond ascertain the value of continuous omalizumab use, whereas non-responders likely have other confounding factors such as poor adherence, persistent allergen exposure or other obstructive airway diseases.[5]

The optimal duration of omalizumab immunotherapy for responders who have benefited remains undetermined. Persistent benefit has been reported after discontinuation of omalizumab. Nopp *et al*. reported that there is no rebound phenomenon in patients whom omalizumab therapy was stopped after being treated for 6 years. Patients reported their asthma control continued to improve or remained unchanged when compared with being on treatment.[14]

In summary, the audit highlights that responders to omalizumab therapy are less likely to experience an asthma exacerbation and hospitalization. They were also more likely to reduce maintenance oral and ICS therapy as well as the need for rescue reliever therapy. These data suggest that omalizumab has proven effective in improving health outcomes for a cohort of carefully selected patients with severe allergic asthma in Ireland.

Conflict of interest: None declared.

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