

Qualitative effects of omalizumab on concomitant IgE-mediated disease in a severe asthmatic population – a real life observational study.

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Abstract

Introduction: Omalizumab is a recombinant humanised monoclonal antibody (anti-IgE) licensed for use in GINA 5 asthma or for chronic idiopathic urticaria. Many patients with asthma have concomitant allergic diseases such as dermatitis and sinusitis. IgE is also implicated in allergic-bronchopulmonary disease (ABPA). In addition, extreme sensitivity to allergen can prevent the initiation of allergen immunotherapy.

Aim: The aim of this study was to assess the efficacy of omalizumab on symptoms of concomitant non asthmatic IgE-mediated allergic disease in a population of severe GINA 5 in a real life observational setting.

Design: This study is a retrospective, observational study assessing patients reported allergic, non-asthmatic symptom response to omalizumab treatment.

Methods: 56 severe asthmatics treated with omalizumab were studied. 37 patients had concomitant rhino-sinusitis, 13 had dermatitis and 4 ABPA.

Subjects were asked to grade the improvement in their symptom scores on an analogue scale from 0 (no response) to 10 (excellent response).

Results: Mean improvement from baseline was 5 and 1.8 in patients with allergic rhino-sinusitis and dermatitis, respectively. Mean improvement from baseline in respiratory symptoms in patients with ABPA was 4.0.

Conclusions: The results from our study suggest that omalizumab may have a role in allergic disease outside of its current license.

Introduction

Omalizumab is currently the only anti-IgE agent available for clinical use in asthma. It is licenced for severe GINA 5 allergic asthma and for refractory chronic idiopathic urticaria. (1) It is an IgG4 anti-IgE mAB that competitively binds to and forms complexes with free IgE at the same C3 binding site that IgE binds to both the high affinity IgE receptor on mast cells and basophils (FCεR1) and the low affinity IgE receptor (FCεR2) on other immunomodulatory cells. This leads to down regulation of these receptors over a period of 12-16 weeks.(2) It has been shown to be effective in reducing hospital admissions, adverse effects and symptom scores in severe asthma. It is approved by NICE for this indication. In our hospital population we have previously shown that omalizumab is effective in reducing exacerbation rate and hospital admissions in patients with severe asthma.(3)

Many patients with asthma have other concomitant IgE –mediated diseases such as rhino-sinusitis and dermatitis. In addition, IgE has been implicated in other inflammatory conditions such as ABPA.(4) In view of the expense of this treatment there is a dearth of clinical information on the effectiveness of omalizumab outside of its primary licenced indications. We felt that a pragmatic study examining the effectiveness on omalizumab on non-asthmatic IgE-mediated disease would be of real life clinic interest and add to the IgE neutralisation therapy debate.

Aim

The aim of this real life observational study was to assess the efficacy of omalizumab on symptoms of concomitant non asthmatic IgE-mediated allergic disease in a population of severe GINA 5 asthmatics.

Methods

We studied 56 with severe GINA 5 allergic asthma who were given omalizumab. 49 were deemed responsive to therapy at 16 weeks whereas 7 did not respond and omalizumab therapy was discontinued. 37 patients had concomitant rhino-sinusitis, 13 dermatitis and 4 ABPA.

All patients underwent a detailed questionnaire by the principle author. Patients gave verbal consent to be included in this study. Patients with rhino-sinusitis and dermatitis were asked to grade their non-asthmatic symptom response on a qualitative analogue scale whereby 0 = no response to a maximum response of 10 (excellent response to omalizumab). Patients with ABPA were asked to grade their asthmatic symptoms on the same scale. Dosage of omalizumab was as per the manufacturer's guideline for the primary asthma indication in all 56 patients based on IgE levels and weight in kilograms.

The data was analysed using the statistical package for social science (SPSS V21). Data was presented as scatterplot graphs below. Patients' baseline symptom score for rhino-sinusitis, dermatitis and asthmatic symptoms was recorded as 0. Patients' subjective recording of change in their symptoms on omalizumab treatment was recorded as 0 if no change in symptoms, positive if improvement of symptoms, and a negative score if worsening of symptoms compared to baseline. Paired-samples t-tests were conducted to evaluate the change in patients symptom scores post omalizumab treatment. A p value of ≤ 0.05 was considered statistically significant.

Results

Table 1 illustrates the demographics of patients (n=56) treated with omalizumab for severe asthma with concomitant IgE mediated disease. 37 patients had concomitant allergic rhino-sinusitis, 13 had allergic dermatitis, 4 ABPA, 2 patients with extreme allergen sensitivity preventing AIT. Patient age ranged from 14 to 76. The mean IgE level pre omalizumab treatment was 346 IU/ml. The mean positive skin prick test result was 2 out of 7 (range 0 – 7). The mean overall duration of omalizumab therapy was 36 months (range 4 – 90 months).

Figure 1 shows the effect of omalizumab on 37 patients' concomitant rhino-sinusitis symptoms with an overall improvement of 5. 28 out of 37 patients had an improvement in their rhino-sinusitis symptoms on omalizumab, with 9 patients reported no response. No patients reported a deterioration of their symptoms on omalizumab. 22 out of 37 patients reported a ≥ 5 improvement score in their rhino-sinusitis symptoms on omalizumab. Using a paired-samples t-test there was a statistically significant improvement in patients allergic rhino-sinusitis symptoms on omalizumab ($p < 0.001$, $n = 37$, mean change of 5, standard deviation 3.6).

Figure 2 illustrates the effect of omalizumab on 13 patients' concomitant dermatitis symptom score with a mean improvement of 1.8. 9 patients out of 13 reported no response, with 4 patients reported an improvement in their symptoms. No patients reported deterioration in their dermatitis symptoms on omalizumab. Only 2 patients out of 13 in the dermatitis group reported a ≥ 5 improvement score in their dermatitis symptoms on omalizumab. Using a paired-samples t-test there was no statistically significant improvement in patients allergic dermatitis symptoms on omalizumab ($p = 0.073$, $n = 13$, mean change of 1.8, standard deviation 3.2).

Figure 3 illustrates the effect of omalizumab on asthmatic symptom score in 4 patients with ABPA. Patients with ABPA reported a mean improvement of 4.0

in their respiratory symptoms. No patients reported a dis-improvement in their asthmatic symptoms on omalizumab. 3 patients out of 4 reported an improvement in their asthmatic symptoms on treatment, with 1 patient reporting no change. 2 patients out of 4 reported a ≥ 5 improvement in their asthmatic symptom score on omalizumab. Using a paired-samples t-test there was not a statistically significant improvement in patients with ABPA's asthmatic symptoms on omalizumab ($p = 0.098$, $n = 4$, mean change of 4.0).

Discussion

Our study has shown that omalizumab is effective in treating concomitant allergic rhinitis and dermatitis in patients with severe allergic asthma in a real observational study. In addition, it improved asthmatic symptoms in patients with ABPA.

IgE is central to the pathogenesis of the allergic diseases asthma, rhinitis, dermatitis, food allergy and anaphylaxis. (7) It has also been implicated in the pathogenesis of the fungal hypersensitivity ABPA.(4, 6) The discovery of the central pathogenic role of IgE in asthma is a triumph of translational medicine. In the early 1900s anaphylaxis, as described by Portier and Richet, became a central problem to biologists when generating prophylactic vaccines for infectious diseases such as diphtheria and tetanus in experimental animals.(8) When these animals received their second dose of toxin after a latency period of c.10 days, instead of becoming tolerant or protected against the toxin, they developed anaphylaxis. It was also seen in humans in cases of food allergy in particular.

The major features of anaphylaxis included wheeze, low blood pressure and invariably death. It was subsequently discovered that anaphylactic activity, was antigen-specific, required a latency period for sensitisation to develop, could be passively transferred by either blood transfusion or via serum, was fixed to

tissue and mediated in part by histamine. Indeed the centrality of acute wheeze led to the novel concept at the time that asthma was indeed an anaphylactic phenomenon, a concept that gained increasing credibility throughout the early 20th century. As asthma was a major feature of hay fever and acute allergic reactions to foods, a conceptual convergence around the pathogenesis of these diseases developed at the time. Indeed, anaphylactic activity was soon discovered in all of these diseases and became known as reagin or reaginic activity. Reagin was subsequently isolated as the antibody IgE in 1967.(9) Furthermore Burrows showed in 1989 that most asthmatics and patients with allergic rhinitis had high IgE levels when corrected for age and gender.(10) The effectiveness of omalizumab in asthma has proven the concept that IgE is centrally pathogenic to this condition.

We reasoned that omalizumab would be effective in other non-asthmatic IgE-mediated diseases. To address this we studied its effectiveness in concomitant allergic diseases in a population of severe asthmatics treated with omalizumab for the primary indication of asthma. We chose this approach because of the high cost associated with the treatment per severe asthmatic patient per year, the fact that the treatment is not licenced for these concomitant conditions, and because of the dearth of information relating to anti-IgE therapy in these concomitant conditions. In the Irish setting omalizumab can cost from €6000 to €47000 depending on patient's IgE level and body weight. Taking an average cost of €25,000 per person per 12 months, with 56 patients and an average treatment time of 36 months, this study would have cost €4,200,000. No large randomised controlled trials have been financed to assess omalizumab in non-asthmatic allergic disease and therefore we currently have to rely on clinical evidence and small trials. We understand that this is a retrospective, subjective study it is still important as it shows that omalizumab is clinically effective in the clinical setting for non-asthmatic allergic disease supporting current

evidence. Due to the high cost of producing a similar prospective study this may not be funded or feasible going forward and thus physicians may be limited to small trials and case studies to support their use of omalizumab outside of current guidelines.

Our study shows that omalizumab therapy can be beneficial outside of its current use. We have proven that omalizumab statistically improves the symptoms of allergic rhino-sinusitis. It improved the asthmatic symptoms in patients with ABPA however this was not statistically significant due to small numbers of patients. Furthermore we have shown that omalizumab can improve symptoms of allergic dermatitis in a small amount of patients although this is not statistically significant.

Both allergic rhino-sinusitis and dermatitis appear to have a common IgE pathway however there appears to be heterogeneity in their response to treatment. In allergic rhinitis there is clear evidence to suggest its role in severe non responsive disease however for allergic dermatitis there is data which shows both a positive and neutral response to omalizumab treatment.(2) The clinical course of allergic dermatitis has not consistently shown to be significantly affected by omalizumab treatment in small trials and case reports.(11, 12) It has been suggested that omalizumab may be effective in higher doses than that licensed for use with asthma, however no large randomised controlled trials have taken place to date, and there are no guidelines for dosing in allergic dermatitis.(12) This study suggests that despite their common pathway, omalizumab is not as effective a treatment for allergic dermatitis as it is for rhino-sinusitis as per current treatment guidelines.

Although the study is limited in that the assessments are subjective and semi-qualitative we feel it adds important new insights to the debate surrounding the clinical effectiveness of anti-IgE therapy in allergic diseases. A particular

strength of the study is large cohort of asthmatics with concomitant allergic diseases that have been on prolonged omalizumab therapy.

We feel this study will be of interest across multiple specialties. It will be relevant for Ear Nose and Throat specialists for the treatment of severe refractory allergic rhinitis, dermatologists for allergic dermatitis, and physicians with an interest in ABPA.

Figure Legend

Figure 1: The effect of omalizumab on patients' concomitant rhino-sinusitis symptoms. N = 37. Patients were asked to grade their symptoms response on a qualitative subjective scale whereby 0 = no response to a maximum response of 10 (excellent response) to omalizumab. 9/37 patients reported no response in their symptoms on omalizumab; 28/37 patients reported an improvement. No patient reported a deterioration of their symptoms on omalizumab. 22/37 patients reported a ≥ 5 point improvement score in their symptoms on omalizumab. There was a statistically significant improvement in patients allergic rhino-sinusitis symptoms on omalizumab using a paired samples t-test ($p < 0.001$, $n = 37$, mean change of 5).

Figure 2: The effect of omalizumab on patients' concomitant dermatitis symptoms. N = 13. Patients were asked to grade their symptoms response on a qualitative subjective scale whereby 0 = no response to a maximum response of 10 (excellent response) to omalizumab. 9/13 patients reported no response in their symptoms on omalizumab. 4/13 patients reported an improvement. No patients reported a deterioration of their symptoms on omalizumab. 2/13 patients reported a ≥ 5 point improvement score in their symptoms on omalizumab. There was no statistically significant improvement in patients allergic dermatitis symptoms on omalizumab using a paired samples t-test ($p = 0.073$, $n = 13$, mean change of 1.8).

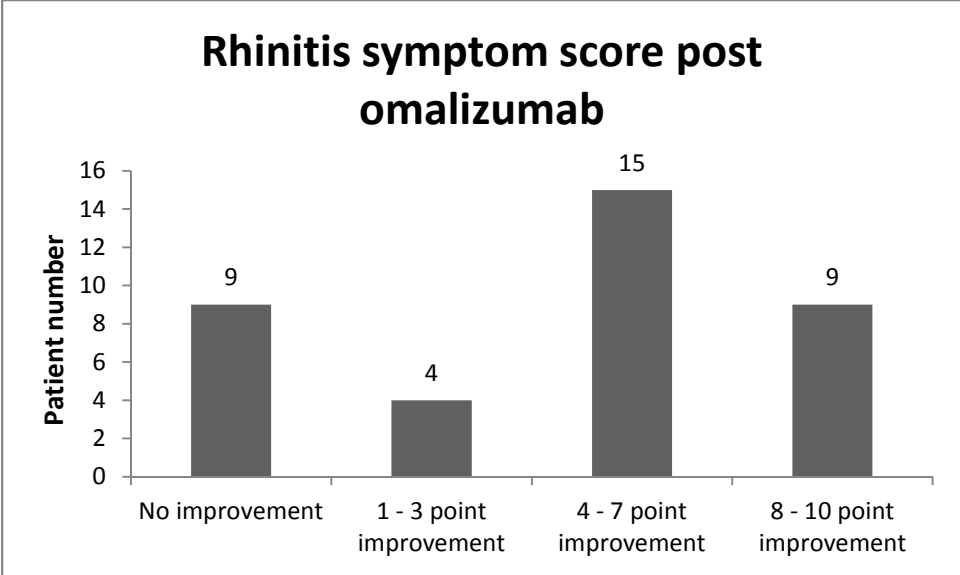
Figure 3: The effect of omalizumab on patients' concomitant asthmatic symptoms. N = 4 Patients were asked to grade their symptoms response on a qualitative subjective scale whereby 0 = no response to a maximum response of 10 (excellent response) to omalizumab. 1/4 patients reported no response in their symptoms on omalizumab. 3/4 patients reported an improvement. No patients reported a deterioration of their symptoms on omalizumab. 2/4 patients reported a ≥ 5 point improvement score in their symptoms on omalizumab. Patients with ABPA reported a mean improvement of 4.0 in their respiratory symptoms. There was no statistically significant improvement in patients with ABPA's asthmatic symptoms on omalizumab using a paired samples t-test ($p = 0.098$, $n = 4$, mean change = 4.0).

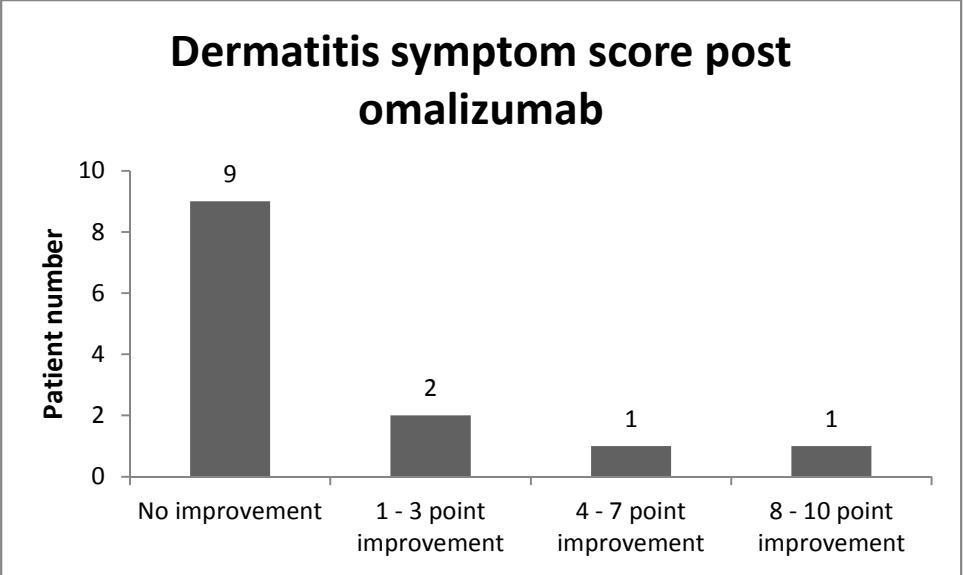
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Table 1: Illustrates the demographics of patients treated with omalizumab for severe asthma with concomitant IgE mediated disease. A positive skin prick test was deemed induration of greater than 2 x 2 mm for 7 common allergens (dust, grass pollen, tree, cat, dog, horse and aspergillus). ABPA, allergic bronchopulmonary disease.

N =	56
Male: Female	26 : 30
Age range in years	14 – 76
Positive skin rick test range	0 – 7 (mean = 2)
Mean IgE pre-treatment	346 IU/ml
Omalizumab treatment length range in months	4 – 90 (mean 36 months)
Concomitant disease:	
• Allergic rhino-sinusitis	37
• Allergic dermatitis	13
• ABPA	4





ABPA symptom score post omalizumab

