Original Research

Omalizumab Treatment for Severe Atopic Asthma in a Real World Montréal Cohort

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Abstract

Background: Severe atopic asthma is poorly controlled with standard treatments, including optimally dosed corticosteroids. A humanized monoclonal antibody binding immunoglobulin E, omalizumab, is approved by the US Food and Drug Administration to treat poorly controlled asthma with elevated serum IgE levels. Its therapeutic efficacy is primarily attributed to reduction of serum-free IgE and through reducing the expression of high-affinity IgE receptors[1].

Objective: The purpose of this case series study was to determine omalizumab's effectiveness in reducing exacerbations in clinical practice. The primary outcome was number of asthma exacerbations requiring oral corticosteroid treatment in the 2-years pre-treatment period compared to 2-years post-treatment. The secondary outcome was cumulative prednisone use 2 years pre-treatment compared to 2-years post-treatment. The amount of inhaled corticosteroid used in beclomethasone equivalents (mcg) was compared 2-years pre-treatment vs. 2-years post-treatment. The patients were stratified based on smoking status and data were analyzed according to subgroups: non-smoker, ex-smoker, and smoker. Lastly, the change in number of exacerbations (pre-treatment vs. post-treatment) was examined as a function of IgE level and blood eosinophilia count.

Methods: Patient data were retrieved with ethics approval (n=32) through hospital records of patients treated at the Montreal Chest Institute of the McGill University Health Center. Medical records including prescription data, emergency triage forms, hospital day admission forms, and progress notes were used. Data were analyzed 2 years before treatment start date and compared to 2 years after.

Results: There was a significant reduction in average number of exacerbations per patient from 6.2 +/- 4.9 pre-treatment to 3.2 +/- 3.2 post-treatment ($p<0.0002$) following institution of omalizumab. There was also a reduction in average cumulative prednisone use per patient from 2504mg to 1423mg ($p<0.002$). There was no significant reduction in inhaled corticosteroid use. There was no correlation between either IgE levels or blood eosinophilia level with change in number of exacerbations.

Conclusions: Omalizumab was effective in reducing the number of exacerbations and prednisone use for patients with severe refractory asthma in clinical practice.

Omalizumab, atopic asthma, severe asthma, case series, exacerbation reduction, monoclonal antibody therapy

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Introduction

Atopic asthma is triggered by a wide range of allergens in the environment[1]. Individuals with severe atopic asthma remain symptomatic despite the use of high dose inhaled corticosteroid treatment and suffer from frequent exacerbations [2]. Patients with severe asthma have the highest hospital morbidity and mortality and account for substantial health care costs through unscheduled doctor visits, hospital admissions, and corticosteroid side effects[6]. Although patients with severe asthma make up only 5% of the asthmatic population, care for these patients represents >50% of total asthma related health care costs[3]. Severe atopic asthma is treated with a combination of high dose inhaled corticosteroids and long-acting bronchodilators but can be controlled with oral corticosteroids, which have more potent anti-inflammatory effects[4]. However, the long-term consequences of such treatments, such as Cushing syndrome, are serious and have motivated the search for alternative and less toxic medications[4]. In 2003, omalizumab, a recombinant monoclonal antibody of immunoglobulin E (IgE) was approved to treat severe asthma in those 12 years of age and older who were inadequately managed by inhaled corticosteroids[5]. Since 2006 the age has been lowered to 6 years. Omalizumab is currently being used as an add-on treatment for severe asthma[5].

High IgE levels induce atopic asthma by binding to mast cells via Fc epsilon receptors, and upon subsequent exposure to an allergen, promote cross-bridging of allergen-specific IgE on the surface of mast cells[7]. In response to this cross-bridging, pro-inflammatory molecules, such as leukotrienes and prostaglandins are synthesized de novo. Chemokines and cytokines are then released and produce the typical allergic inflammatory response[7]. Chronic inflammation and airway remodeling leads to a hyperresponsive bronchial tree that narrows in response to chemokine and cytokine release, causing bronchospasm. Cigarette smoke and other inhaled toxins contain chemicals that damage respiratory epithelium and may exacerbate inflammation in asthmatics[20]. Eosinophils are often found in increased numbers in serum and sputum in asthmatic patients, usually in relation to severity of asthma[1]. Omalizumab reduces serum concentration of IgE, preventing it from binding to high affinity Fc epsilon receptors, therefore limiting the allergen cascade[6]. As a therapeutic agent, it targets the underlying inflammatory pathways causing asthma, rather than simply controlling symptoms. Additionally, omalizumab owers the number of high affinity IgE receptors over time through down regulation of the Fc epsilon receptors[8]. Clinical studies have shown that in addition to a significant reduction in IgE levels, omalizumab also reduces sputum and serum eosinophilia and serum interleukin 4 (Il-4) levels[7].

Although several clinical trials have established that omalizumab is efficacious under controlled clinical settings[2, 5, 9], fewer studies have addressed its use in clinical practice[10]. This study assessed whether prescribing omalizumab in a university hospital asthma clinic led to results that were comparable to the published literature.

Methods

Forty-one (41) patients treated with omalizumab at the Montreal Chest Institute of the McGill University Health Centre were identified for the study. Ethics approval was obtained through the Ethics Review Board of the McGill University Health Centre. Data were extracted from patient medical records including prescription data, emergency triage forms, hospital day admission forms, and progress notes. The American Thoracic Society's definition of exacerbation was used, which includes: (a) Use of systemic corticosteroids (tablets, suspension, or injection) with an increase from a stable maintenance dose, for at least 3 days or (b) a hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids[(1)]. Courses of corticosteroids separated by 1 week or more were treated as separate exacerbation events.

Exacerbations were identified through emergency visit records, hospital day charts, and progress notes. Total prednisone use was calculated based on prescribed action plans, hospital records, and patient reporting. The average number of exacerbations during the 2-year pre-treatment phase and 2-year post treatment phase was determined. The average amount of prednisone used (mg) during the 2-year pre-treatment phase and 2-year post treatment phase was also determined. Total prescribed inhaled corticosteroid use was calculated based on total amounts from prescriptions in the 2-year pre and 2-year post treatment periods. All inhaled corticosteroids were converted to beclomethasone equivalents (mcg)[11]. A conversion factor of 1.25 was used to convert methylprednisolone to prednisone equivalents[11].

Smoking status, IgE levels (pre-treatment) and blood eosinophil count (pre-treatment) were also

obtained. Demographic information included age, sex and body mass index (BMI).

Smoking status was determined from hospital records and omalizumab registration forms. Patients were classified as: smoker, non-smoker, or ex-smoker. Patients smoking any number of cigarettes on a daily basis qualified as a smoker. Ex-smokers had not smoked in the year prior.

Statistical Analysis

Data, including number of exacerbations, prednisone use (mg) and inhaled corticosteroid use in beclomethasone equivalents (mcg) in pre and post-treatment periods were analyzed using a paired two tailed t-test with a threshold significance set at $p<0.05$. The outcomes were compared within the same patient data. Data are shown as means +/- standard deviation. A correlational coefficient was used to measure the relationship between i) IgE level and ii) Eosinophil level and change in number of exacerbations. The average number of exacerbations per year in the 12-24 months preceding treatment was compared to 12-24 months after treatment using paired two tailed t-tests with significance level of $p<0.05$.

Results

Subjects and baseline characteristics

Forty-one (41) patients with severe asthma who were treated with omalzumab at the Montreal Chest Institute were identified. One patient had an allergic reaction to omalizumab and discontinued treatment; therefore their data was omitted from the study. Eight patients were not included in the 2-year post treatment group due to incomplete data based on treatment start date. Total number of study participants in this study was 32 (n=32).

Effect of omalizumab on asthma exacerbations

There was a significant reduction in the average number of exacerbations with omalizumab from 6.2 +/- 4.9 in the 2y pre-treatment period to 3.2 +/- 3.2 in the 2y post treatment period ($p<0.0002$; Figure 1A). When comparing the effects of treatment with omalizumab on exacerbation rates in non-smokers, ex-smokers and current smokers there was a significant reduction in rates among non-smokers ($n=19$, $p<0.02$) and ex-smokers ($n=9$ $p<0.02$) but not in current smokers ($n=4$, $p>0.05$) (Figure 1B).

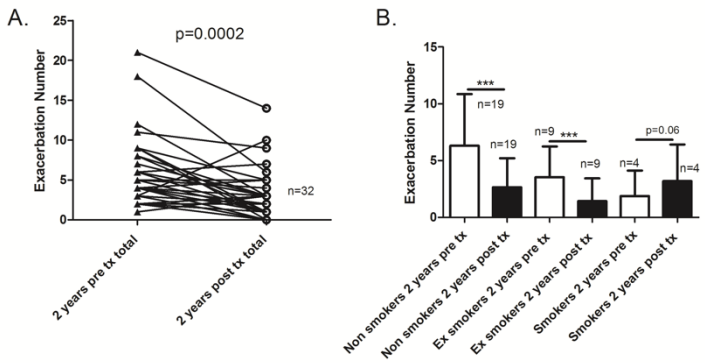

Figure 1- **A.** Average number of exacerbations 2 years pre omalizumab treatment vs. 2 years post treatment **B**. Average number of exacerbations 2 years pre omalizumab treatment vs. 2 years post treatment in non-smokers, ex-smokers, and smokers.

The average number of exacerbations per year was compared in the 12-24 months preceding treatment (2.64) compared with 12-24 months after treatment (1.88). The reduction in number of exacerbations comparing these two time periods was not significant ($p>0.05$).

Effect of omalizumab on corticosteroid use

There was a significant reduction in average prednisone use from 2508mg in the pre-treatment period compared to 1399mg in the post-treatment period (Figure 2A; $p<0.002$). There was no significant reduction in average prednisone use when comparing smokers, ex-smokers, and non-smokers (Figure 2B, $p>0.05$ for all groups).

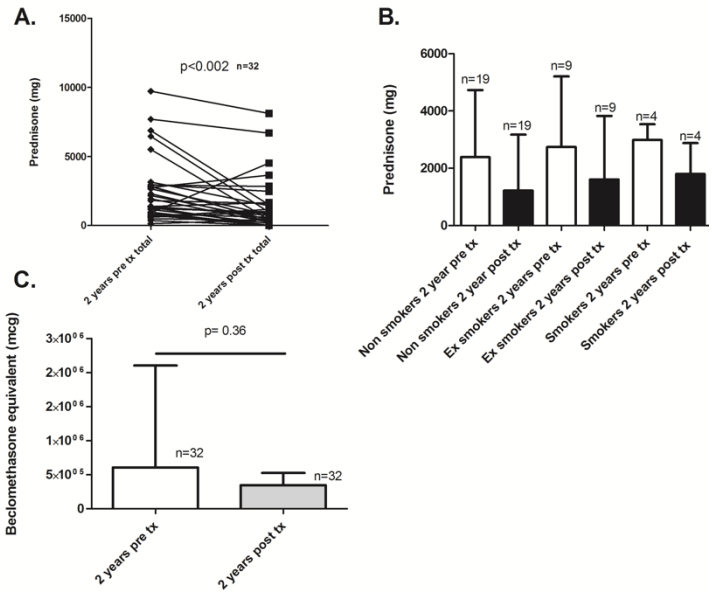

Figure 2 - **A**. Average prednisone use 2 years pre omalizumab treatment vs. 2 years post treatment **B**. Average prednisone use 2 years pre omalizumab treatment vs. 2 years post treatment in non-smokers, ex-smokers, and smokers **C**. Average beclomethasone use 2 years pre omalizumab treatment vs. 2 years post treatment

Effect of omalizumab on inhaled corticosteroid use

There was no significant reduction in total inhaled corticosteroid therapy in beclomethasone equivalents (mcg) in the pre-treatment period compared to post-treatment (Figure 2C; p=0.36).

Relationship between IgE level and change in exacerbations

Pre-treatment IgE level had no relationship with change in number of exacerbations over the treatment period. The coefficient of determination showed no correlation between these two variables (R^2= 0.037, p>0.05, Figure 3A).

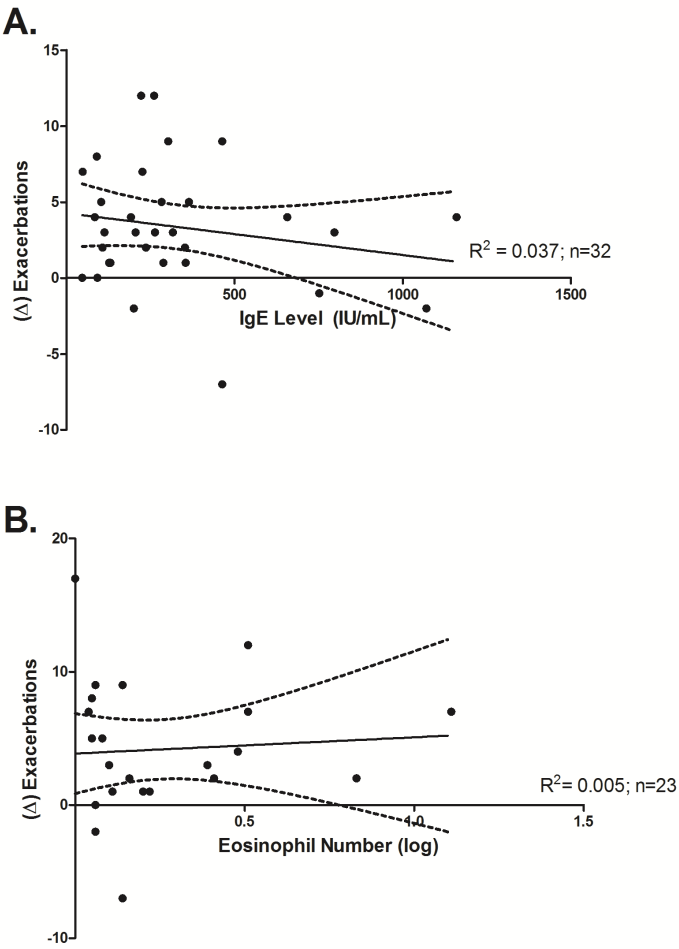

Figure 3. A. Change in number of exacerbations as a function of IgE level (IU/mL) **B**. Change in number of exacerbations as a function of eosinophil number

Relationship between blood eosinophils and change in exacerbations

Pre-treatment eosinophil level had no relationship with change in number of exacerbations over the treatment period. The coefficient of determination showed no correlation between these two variables (R^2=0.005, p>0.05, Figure 3B). 9 patients did not have eosinophil levels ordered, therefore n=23 for Figure 3B.

Discussion

The collection of patient data over four years enabled the analysis of outcomes in a Montreal patient cohort suffering from uncontrolled allergic asthma. We found that there was a significant reduction in exacerbations and prednisone use following omalizumab treatment for patients with severe refractory asthma. The reduction in inhaled corticosteroid use was not significant. The relative treatment benefit among smokers, non-smokers, and ex-smokers cannot be adequately assessed due to small sample sizes. Baseline levels of serum IgE and blood eosinophil level did not correlate with a change in number of exacerbations.

Since the introduction of omalizumab more than a decade ago there are many studies describing its efficacy in controlled settings. However, a recent review stressed the need for more studies on omalizumab's effect in the severe atopic asthma group[5]. A meta-analysis performed on three randomized, double-blind, placebo-controlled studies that enrolled 1412 patients with moderate or severe allergic asthma showed an average reduction in exacerbations of 35% in a treatment group compared to 18% in the placebo[6]. Omalizumab also reduces the need for concomitant asthma medication[12] and improves asthma related quality of life (AQoL)[9]. Corren et al found that omalizumab treatment markedly reduced hospitalizations for asthmatic patients[12]. In inner-city children with asthma, omalizumab decreased the number of days with asthma symptoms per 2-week interval by 24.5% and significantly reduced the proportion of participants who had one or more exacerbations from 48.8% to 30.3% [12]. Data from an observational study based on a registry of patients treated with omalizumab found that the proportion of patients with no clinically significant exacerbations in 1 year increased from 6.8% during the 12-month pre-treatment period to 54.1% and 67.3% at months 12 and 24, respectively and there was a marked reduction in prednisone use[10]. About two thirds of patients benefited from treatment.

In the present study, 2 years of omalizumab treatment resulted in a reduction in the following parameters: average number of exacerbations per patient and average prednisone use per patient. Direct comparisons between these results and those of larger

clinical trials should be made with some caution due to small sample sizes. However, previous studies demonstrate similar results, therefore if the sample size were enlarged it appears the data would correlate well with Corren et al's results.

The average number of exacerbations per year was compared in the 12-24 months preceding treatment (2.64) compared with 12-24 months after treatment (1.88). This reduction in number of exacerbations was not significant ($p>0.05$). Therefore, a limitation of this study may be regression to mean bias. Since these two time periods are the ones most distant from the aggravation in symptoms that likely caused the individuals to seek further treatment, they may be, by chance, closer to the "baseline" values for number of exacerbations. Hence, this suggests that after 1 year of initial improvement on the treatment there may be a return to baseline.

The EXCELS observational prospective cohort study demonstrated that 83.0% of patients on the 2-week dosing regimen (n = 152) and 65.0% of patients on the 4-week dosing regimen (n=137) missed at least 1 dose [13]. Hence, non-adherence to the dosing regimen may occur in clinical practice more than clinical trials. Observational studies, such as this case series, are useful to determine outcomes in clinical practice.

The number of exacerbations has been shown to change based on season. Teach *et al* demonstrated that adding omalizumab before return to school to ongoing guidelines-based care reduces fall asthma exacerbations among inner city youth[14]. Examining the rate of exacerbation based on season through retrospective chart review may be a focus of future research. Although asthma and rhinitis are considered components of a single IgE-mediated inflammatory disorder, they are typically treated as independent conditions[15]. Further research may look at omalizumab's effect on rhinitis, nasal congestion, and their interaction with asthma. Although omalizumab is an effective drug, it adds significant costs to the health care system. A cost-effectiveness analysis may be helpful in determining omalizumab's potential for real world use amongst eligible patients[16]. Targeting the appropriate patient for treatment is paramount.

Conclusion

This observational study confirms findings of larger clinical trials that show omalizumab as an effective treatment for severe atopic asthma and provides substantial benefit to patients who are suffering from repeated asthma attacks.

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