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Self-Reported Improvement for Chronic Rhinosinusitis Major Symptoms in Patients Treated with Omalizumab

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Abstract: Objective: To evaluate the clinical effect of omalizumab therapy on the symptoms of patients with chronic rhinosinusitis (CRS). Methods: This cross-sectional study evaluated CRS major symptom improvement in patients with CRS on omalizumab therapy and patients who met omalizumab therapy indications, but could not access coverage for omalizumab. Changes in overall chronic rhinosinusitis symptom burden and each of the major symptoms of CRS were rated on a 10 cm visual analogue scale (VAS). The Mann–Whitney test was used to compare the symptom improvement between groups. Results: Omalizumab therapy provided a mean overall symptom improvement of 69.5% (individual symptom improvement: facial pain 78.5%, nasal obstruction 69.8%, rhinorrhea 56.2%, and olfaction 55.8%). For the control group, mean overall symptom improvement since omalizumab screening was 16.8% (individual symptom improvement: rhinorrhea 16.4%, nasal obstruction 15.3%, no improvement in facial pain or olfaction). Overall, and for each major symptom, improvement was significantly greater for omalizumab treated patients ($p < 0.05$). Conclusion: Omalizumab treatment provided significant improvement in every major clinical symptom of CRS in the treated cohort of patients with recalcitrant CRS, in comparison to the control cohort. A well-designed randomized clinical trial is needed to further assess the efficacy and safety of omalizumab treatment for CRS.

Keywords: chronic rhinosinusitis; omalizumab; anti-IgE; monoclonal antibody; chronic rhinosinusitis with nasal polyps; aspirin exacerbated respiratory disease

1. Introduction

Chronic rhinosinusitis (CRS) is a disease of considerable prevalence, affecting 2–16% of the population in the United States and Canada [1,2]. The direct cost of CRS brings an economic burden of nearly 65 billion dollars in the United States, nearly 1% of the total US healthcare budget in 2011 [2]. CRS is a complex inflammatory disease characterized by persistent inflammation of the paranasal sinuses, with concomitant bacterial colonization [3–8]. The symptoms of this disease negatively affect the physical and psychological wellbeing of patients, thereby decreasing their overall quality of life [3].

Several therapies have been explored for the management of CRS. Therapies range from medical therapies, including saline irrigations, intranasal corticosteroids and antibiotics, to surgical intervention, primarily endoscopic sinus surgery. These therapies focus on symptom control, and although historically effective for symptom relief and inflammatory reduction, they do not target specific underlying disease pathophysiology. Despite maximal therapy, many patients remain symptomatic,

due to inadequate paranasal mucosal inflammatory regulation. Disease control remains especially elusive for patients with nasal polyposis and comorbid asthma [5].

Recently, anti-immunoglobulin E (IgE) therapy has emerged as a potential treatment for CRS. Omalizumab, a recombinant DNA-derived humanized monoclonal antibody that binds to human IgE, has proven to be effective for the management of severe asthma [9,10]. This therapy reduces circulating IgE, thereby interrupting the inflammatory cascade and subsequent release of proinflammatory mediators. [9] Omalizumab is currently approved for use in patients 12 years or older with moderate to severe persistent allergic asthma and inadequately controlled symptoms with inhaled corticosteroids [2]. Interestingly, inflammation in asthma and nasal polyps share features, such as airway eosinophilia, local IgE formation, and a TH2 cytokine profile [10]. Growing evidence has demonstrated that omalizumab may be beneficial in treating other allergic diseases outside of asthma, such as CRS and allergic rhinitis [10,11].

Current evidence for omalizumab use in treating CRS is inconclusive. Two small randomized control trials (RCT) showed that omalizumab reduced polyp size and improved sinus inflammation [10,12]. However, a recently conducted systematic review concluded that there has yet to be a demonstrated benefit for CRS patient quality of life with omalizumab use, and the current literature has a moderate risk of bias for any recommendations regarding anti-IgE monoclonal antibody therapy for the treatment of CRS [3]. Clearly, further research to explore the implications of anti-IgE therapy on CRS is therefore needed.

The purpose of this study was to perform a real-world evaluation of the clinical effect of anti-IgE monoclonal antibody therapy on sinus symptom and disease control for patients with recalcitrant CRS receiving anti-IgE therapy.

2. Materials and Methods

2.1. Study Design

This study was conducted as a non-concurrent cross-sectional cohort study. This study was reviewed and approved by IRB Services, an independent research ethics board.

2.2. Study Population

Patients with asthma, who met the therapy indications for omalizumab and were assessed in order to initiate therapy, and who also had CRS, were included in this study. Within this group of patients, two subgroups were identified: asthma with CRS patients who were receiving omalizumab therapy (treatment) and asthma with CRS patients who were not receiving omalizumab therapy, due to lack of insurance coverage for omalizumab (control). Both patient groups had had failed surgical and/or medical therapy for CRS.

2.3. Data Collection

Demographic and medical history data were collected from the patient's medical chart. Data extraction targeted demographic details, smoking status, asthma, environmental allergy and CRS specific disease related data. Smoking status was divided into past smoker, current smoker, and never smoker categories. Allergy specific data collected included allergies (as determined by skin prick testing) to dust mites, cats, dogs, trees, ragweed, and grasses. CRS specific data collected was comprised of the following categories: aspirin exacerbated respiratory disease (AERD), sinusitis phenotype (CRS with nasal polyps (CRSwNP), and CRS without nasal polyps (CRSsNP)), history of previous sinus surgery, and current topical steroid treatment for CRS.

2.4. Outcome Measures

Patients were instructed to use a 10 cm visual analogue scale (VAS) to rate (1) the change in overall chronic rhinosinusitis symptom burden and (2) the change in each of the major symptoms of CRS since

being assessed (control group) or having started omalizumab therapy (treatment group). The major symptoms CRS patients were asked to rate were "sense of smell", "facial pain", "nasal blockage" and "rhinorrhea".

2.5. Statistical Analysis

The Mann–Whitney test was used to compare the symptom improvement between groups.

3. Results

3.1. Study Population

There were 25 patients in the treatment group, and 5 patients in the control group. The mean treatment duration within the treatment group was 19 months. Moreover, 76% (19) of patients in the treatment group, and 80% (4) of patients in the control group had nasal polyps. The characteristics of the included patients are shown in Table 1.

Table 1. Patient Characteristics.

Variable	Omalizumab	Control
Patients *n*	25	5
Male: Female	11:14	3:2
Smoking n (%)		
Past smoker	10(40)	4(80)
Current smoker	2(8)	1(20)
Never	13(52)	
Allergies * n (%)		
Dust mites	25(100)	5(100)
Cat	15(60)	2(40)
Dog	10(40)	1(20)
Trees	12(48)	3(60)
Ragweed	13(52)	2(40)
Grasses	12(48)	6(60)
AERD ** *n* (%)	8(32)	3(60)
Sinusitis Dx n (%)		
CRSwNP	19(76)	4(80)
CRSsNP	6(24)	1(20)
Previous Sinus Surgery *n* (%)	18(72)	4(80)

* AERD: Aspirin exacerbated respiratory disease, ** Confirmed by skin prick test.

All patients were being treated for CRS with topical medication—either intranasal corticosteroids (INCS) or budesonide irrigations (see Table 2)—for at least 6 months consecutively, with the majority of patients using budesonide-saline irrigations.

Table 2. Treatment for Chronic Rhinosinusitis.

Medication	Omalizumab	Control
Budesonide irrigations *	13(52)	3(60)
Intranasal Corticosteroids **	8(32)	2(40)
Both (alternating)	4(16)	-

* 0.5mg/mL, 2 mL nebule in 240 mL of saline, ** doses range from 200–400 mcg/day.

3.2. Outcome Measures

Omalizumab therapy provided a mean overall chronic rhinosinusitis symptom burden improvement of 69.5% (individually: facial pain 78.5%, nasal obstruction 69.8%, rhinorrhea 56.2%,

and olfaction 55.8%). For the control group, mean overall chronic rhinosinusitis symptom burden improvement since omalizumab screening was 16.8% (individually: rhinorrhea 16.4%, nasal obstruction 15.2%, and no improvement in olfaction or facial pain). Symptom improvement was significantly greater for omalizumab treated patients in every category ($p < 0.05$; see Figure 1).

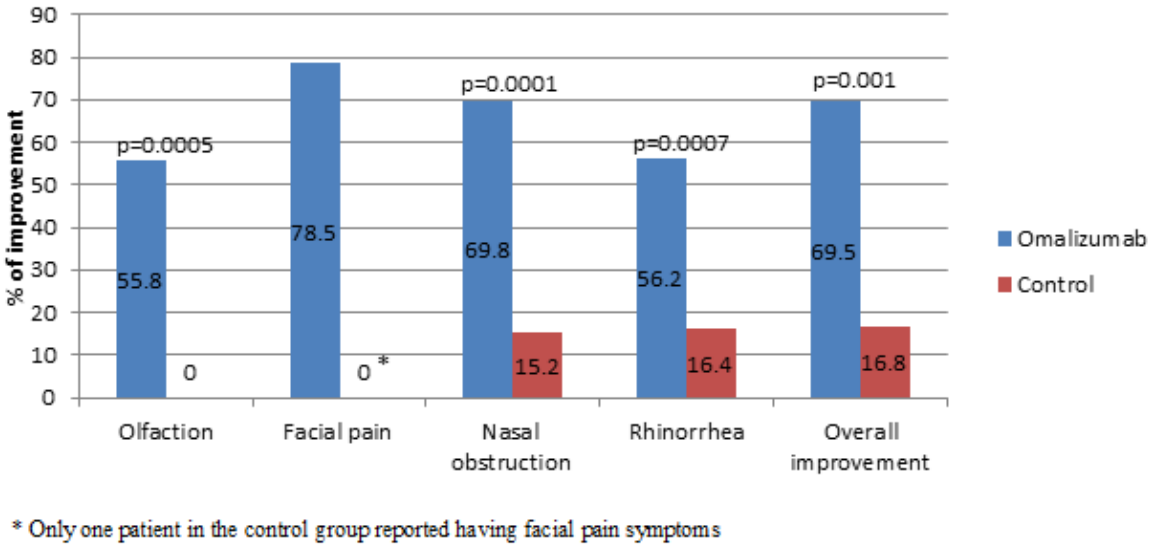

Figure 1. Patient reported symptom improvement of chronic rhinosinusitis.

3.3. AERD

Within the subgroup of patients with AERD, a significant improvement was found for nasal obstruction ($p = 0.05$) and olfaction ($p = 0.03$), but not for rhinorrhea, nor for overall improvement in chronic rhinosinusitis symptom burden ($p = 0.5$ and $p = 0.1$, respectively) for patients receiving omalizumab therapy. Within the group treated with omalizumab, there were no significant differences for symptom improvement in any of the symptom categories when comparing patients with CRSwNP to those with AERD.

4. Discussion

This real-world study found that patients with severe CRS with asthma reported significant improvement in all of their sinonasal symptomatology after being treated with omalizumab monoclonal antibody therapy. These results are consistent with a similar retrospective study, in which twenty-eight out of 37 patients reported improvement in their CRS symptoms, and 22 out of 37 patients reported a ≥5 (0–10) improvement in their CRS symptoms after omalizumab [13]. A recent retrospective study has shown that treatment with omalizumab can result in a reduction of antibiotic use for patients with CRS, and a potential reduction in steroid use in a subset of CRS patients [14].

In the current study, a subgroup analysis of patients with AERD showed that an improvement in nasal obstruction and olfaction was significantly greater in the treatment group. Furthermore, an analysis of this group found that the overall symptom improvement did not differ between AERD and the CRSwNP. That is, patients with AERD received the same benefits as patients with CRSwNP without aspirin sensitization. Therefore, for this severe variant of CRSwNP, omalizumab may represent a rescue treatment for the AERD subgroup, that is notoriously difficult to treat due to the severity of the paranasal sinus mucosal inflammation.

Despite the positive results of observational studies, the evidence provided by the randomized clinical trials that have examined the role of omalizumab in CRS are inconclusive [3,10,12]. Two small randomized controlled trials (RCT) have shown that omalizumab reduces polyp size and improves sinus inflammation [10,12]. Gevaert et al. (2013) [10] conducted a randomized, double-blind, placebo-controlled study of allergic and nonallergic patients with nasal polyps and comorbid asthma,

and found omalizumab to have a beneficial effect on airway symptoms (nasal congestion, anterior rhinorrhea, loss of sense of smell, wheezing, and dyspnea) and on quality-of-life scores, irrespective of the presence of an allergy . In contrast, Pinto et al. (2010) [12] concluded that IgE plays, at most, a small role in the mucosal inflammation of CRS and the symptoms . Furthermore, a recent systematic review evaluating the evidence for anti-IgE monoclonal antibody therapy concluded that there is currently a low overall quality of evidence regarding anti-IgE monoclonal antibody therapy for the treatment of CRS [3]. Clearly, despite the results of these trials, there is still a need for greater evidence for the efficacy of anti-IgE monoclonal antibody therapy in patients with CRS.

The purpose of this study was to provide a real-world assessment of symptom improvement and control achieved with omalizumab monoclonal antibody therapy in patients with CRS, and therefore, patient symptoms were used as primary outcome measures. CRS is a patient symptom driven disease; that is, improved quality of life is the major outcome sought by affected patients. The use of a VAS for the assessment of patient symptomatology in CRS is well supported and reflects the real-world design of the current study [5]. There are objective disease status measurements that can be used to assess response to treatment that we did not include in our design. These measures include the previously reported endoscopic assessments of inflammation and CT scan grading systems for disease severity [10]. The first double-blind randomized control trial published on this topic in 2013 assessed the clinical efficacy of omalizumab in patients with nasal polyps and comorbid asthma, by using the reduction in total nasal endoscopic polyp scores after 16 weeks of treatment as the primary outcome measure, and used changes in the Lund–Mackay computed tomographic (CT) scores as a secondary outcome measure [10]. Other studies have also employed these objective measurement tools [15].

CRS is a chronic disease with high relapse potential [16]. Although our findings are representative of patients who received omalizumab treatment for a mean duration of 19 months, they may not be representative of long-term disease outcomes. Further controlled trials to assess the long-term effectiveness of omalizumab treatment on CRS and disease relapse rates are required, as the utilization of monoclonal antibody therapy comes at a substantial potential health system cost. In addition to assessing long-term treatment effectiveness, longer follow-up periods may also address questions surrounding the safety profile of omalizumab in patients with CRS [3]. In the literature, neoplasia has been reported more frequently in omalizumab-treated patients (0.50%) than in control subjects (0.18%) across all completed studies [15]. However, previous studies focusing on the safety of omalizumab in treatment for children with asthma have concluded that there is an acceptable safety profile in that context [17–19].

Lastly, given the real-world nature of this study, it was not a blinded study, and therefore the potential for biased symptom reporting within the treatment group must be recognized. Symptom improvement assessment was done in a way that it is subject to recall bias. Access to drug coverage insurance was different in the study groups which may have affected the CRS outcomes. Additionally, the sample size for this study is small, and the results may not be representative of all patients treated for asthma with CRS. This further supports the need for a sufficiently powered, well-designed randomized controlled trial addressing the use of this treatment in the CRS population.

5. Conclusions

In comparison to the control group of patients in this study, omalizumab treatment provided a significant improvement in every major clinical symptom of CRS in patients with CRS recalcitrant to surgical and/or maximal medical therapy. Given the available evidence in the literature pertaining to the benefits of omalizumb treatment for CRS, a well-designed randomized clinical trial is needed to further assess the efficacy and safety of omalizumab treatment for CRS. This potential study must be large enough to accommodate an analysis of some of the most difficult-to-manage CRS subtypes, such as AERD.

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