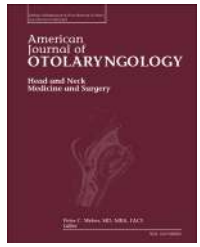
AMERICAN JOURNAL OF OTOLARYNGOLOGY–HEAD AND NECK MEDICINE AND SURGERY XX (2015) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/amjoto



Original contribution

Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate or severe asthma ☆

Eng Cern Gan, MBBS, MRCS (Edin), MMED (ORL), FAMS [a,b,*], *Al-Rahim R. Habib, MSc* [a], *Alykhan Rajwani, BSc* [a], *Amin R. Javer, BSc, MD, FRCSC, FARS* [a]

[a] *Division of Otolaryngology, University of British Columbia, St. Paul's Sinus Centre, 1081 Burrard St., Vancouver, British Columbia, Canada*
[b] *Department of Otolaryngology–Head & Neck Surgery, Changi General Hospital, 2 Simei Street 3, Singapore*

ARTICLE INFO

Article history:
Received 7 April 2015

ABSTRACT

Purpose: 1. To assess the efficacy of omalizumab therapy in improving sinonasal outcomes in refractory allergic fungal rhinosinusitis (AFRS) patients with moderate or severe asthma. 2. To determine if omalizumab therapy reduces the usage of corticosteroids or antifungal therapy in AFRS patients

Method: Design: The clinical charts of patients with AFRS with moderate or severe asthma who received at least three subcutaneous injections of omalizumab therapy between 1st January 2012 and 1st May 2014 were retrospectively reviewed. These patients had undergone bilateral functional endoscopic sinus surgery (FESS) and failed adjunct medical treatments (oral or topical corticosteroids and/or antifungal therapy) prior to omalizumab therapy.

Results: Seven patients met the inclusion criteria and were included in this study. The mean age of the patients was 48.14. The average number of subcutaneous omalizumab injections was 7.57 (range 6–11) with a mean dosage of 287 mg (range 225–375 mg). The mean pre-omalizumab treatment Sino-Nasal Outcome Test-22 (SNOT-22) score was 52.14 while the mean post-omalizumab treatment SNOT-22 score was 35.86 (31% improvement). The mean pre-omalizumab therapy Phillpott–Javer endoscopic score (over the last one year before omalizumab therapy) was 36 while the mean post-omalizumab therapy endoscopic score (from the last clinic visit) was 14 (61% improvement). Omalizumab therapy reduced the dependence of AFRS patients on corticosteroid and antifungal treatments.

Conclusion: Omalizumab therapy can be considered as a potential adjunct for the treatment for patients with refractory AFRS with moderate or severe asthma. However, larger prospective studies to confirm the findings of this study will be required.

☆ Conflict of interests: None.

* *Corresponding author at:* Department of Otolaryngology–Head & Neck Surgery, Changi General Hospital, 2 Simei Street 3, Singapore, 529889. Tel.: +65 6788 8833, +1 604 806 9926; fax: +65 6781 6435, +1 604 806 9690.
E-mail address: engcern@gmail.com (E.C. Gan).

http://dx.doi.org/10.1016/j.amjoto.2015.05.008
0196-0709/

1. Introduction

Allergic fungal rhinosinusitis (AFRS) is a noninvasive form of fungal rhinosinusitis (FRS) [1]. It accounts for approximately 7% of all chronic sinusitis cases requiring surgery [2]. The hallmark of this disease is the presence of thick peanut butter-like allergic mucin in the sinuses with histological findings of degenerating eosinophils, Charcot–Layden crystals and fungal hyphae without the evidence of sinonasal tissue invasion [2]. The typical AFRS patients are young, immunocompetent adults presenting with symptoms of CRS. The benchmark for the diagnosis of AFRS for many years has been the Bent and Kuhn criteria [3]. These include the presence of type I IgE-mediated hypersensitivity, nasal polyposis, characteristic CT findings (double density sign), eosinophilic or allergic mucin and a positive fungal smear [3].

Although AFRS has been recognized as an independent subset of CRS for over 30 years, the pathophysiology remains unknown and controversial. In a literature review by Ferguson et al., two popular theories were found [4]. The allergic (immunologic) theory proposed by Manning et al., was derived from the allergic bronchopulmonary aspergillosis (ABPA) model. They believed that an atopic host exposed to fungi resulted in antigenic stimulation by a combination of Gel and Coomb type I and type III hypersensitivity, leading to an intense inflammatory response [5,6]. The eosinophilic theory was suggested by Ponikou et al. when they demonstrated that eosinophilic chemotaxis in response to extramucosal fungi was the hallmark of the inflammatory reaction in AFRS [7]. The term eosinophilic mucin rhinosinusitis (EMRS) was then coined by Ferguson et al. to describe the non-allergic group of patients who have AFRS-like features in the absence of demonstrable fungal hyphae [4]. Dysregulation of immunologic controls of upper and lower airway eosinophilia was believed to be the underlying mechanism in EMRS.

The first step in the management of AFRS is complete and meticulous functional endoscopic sinus surgery (FESS) to debride and remove all polypoid disease, allergic mucin and fungal debris [2,8]. The aim of FESS is to restore ventilation, improve drainage of the paranasal sinuses and reduce the antigenic stimulus [9,10]. Following this, a combination of adjunct medical treatment is often required to keep the disease in a dormant state. These include topical and systemic corticosteroids and antifungal agents, immunotherapy and nasal rinses. Unfortunately, there is a subset of patients who are refractory to these treatments and the search for a salvage therapy continues.

Omalizumab is a humanized monoclonal anti-IgE antibody that has been shown to be an effective adjuvant therapy in severe atopic asthma, allergic rhinitis, CRS with nasal polyposis (CRSwNP) and asthma and ABPA [11–21]. Omalizumab decreases free IgE levels by binding to free circulating IgE. This process inhibits the binding of IgE to the high-affinity IgE receptors [22]. In addition, omalizumab reduces IgE receptors on mast cells, basophils and dendritic cells [23]. As an increase in local production of IgE is implicated in the pathophysiology of CRSwNP and AFRS [5,6] omalizumab may have a potential benefit in these patients. Furthermore, given the pathophysiological similarity between ABPA and AFRS and recent case reports [14–18] and case series[19] demonstrating improvement in the clinical outcome of omalizumab in ABPA patients, the efficacy of omalizumab in patients with AFRS should be explored. Hence in this study, we aim to compare the sinonasal outcomes before and after omalizumab therapy in patients with refractory AFRS and moderate to severe asthma.

2. Methods

The clinical charts of AFRS patients with moderate or severe asthma who had undergone FESS and failed adjunct medical treatments (topical and systemic corticosteroid and oral itraconazole) between January 2012 and February 2013 were retrospectively reviewed at St Paul's Sinus Centre in Vancouver, Canada. Patients who had received omalizumab during this period were selected for this study. The study received approval from the University of British Columbia Clinical Research Ethics Board. The regimen for medical treatments were as follows: a course of systemic steroid consisted of a tapering dose of oral prednisolone at 40 mg daily for 4 days, followed by 30 mg daily for 4 days, followed by 20 mg daily for 4 days and 10 or 5 mg daily for 1 month; topical steroid used was budesonide respules (0.5 mg/ml × 2 ml) applied through the Mucosal Atomization Device (MAD) in the Mygind position (1 ml in each nostril); oral itraconazole dosage was 100 mg bid for at least 6 weeks duration. The following data were collected form the patients' charts:

1. Patients' demographics and baseline characteristics
2. Change in sinonasal symptoms before and after omalizumab therapy (as documented by the SNOT-22 score)
3. Change in endoscopic mucosal disease before and after omalizumab therapy (as documented by the Phillpott-Javer endoscopic staging for AFRS)
4. Change in the frequency and dosage of adjunct medical treatment postsurgery (oral and topical corticosteroids and antifungal agents) before and after omalizumab therapy
5. Documented side effects from omalizumab therapy.

The Philpott–Javer endoscopic staging system (Fig. 1) is a validated system that was derived from modifications made to the Kupferberg endoscopic staging system [24]. Each sinus cavity and the olfactory cleft are scored independently on a scale from 0 to 9 based on the degree of mucosal inflammation. An additional 1-point is allocated for each sinus if allergic mucin is noted grossly. This allows for a maximum score of 10 points per sinus cavity, 50 points for each side of the nose (including the olfactory cleft) and 100 points for the total maximum bilateral score. Such a system is much more sensitive and allows for much better tracking of disease control postoperatively.

2.1. *Statistical analysis*

Demographic and baseline characteristics were extracted from patient charts and recorded for each subject.

Please cite this article as: Gan EC, et al, Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate..., Am J Otolaryngol–Head and Neck Med and Surg (2015), http://dx.doi.org/10.1016/j.amjoto.2015.05.008

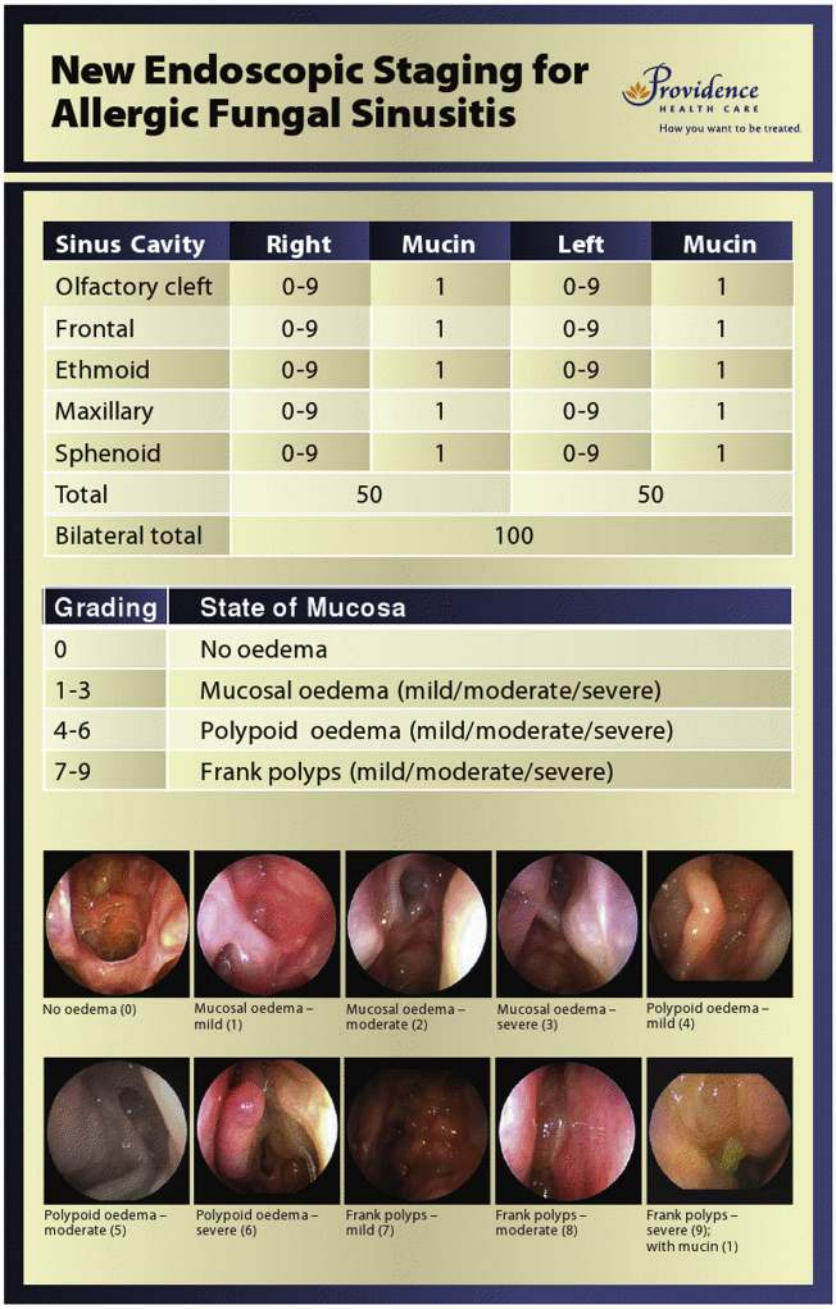


Fig. 1 – The Philpott–Javer endoscopic staging system.

Demographic data included age (years), sex, history of smoking and race. Baseline characteristics included presence or absence of asthma, forced expiratory volume in one second (FEV_1), immunoglobulin-E level (IU/ml), SNOT-22 and endoscopic score (Philpott–Javer) immediately prior to receiving treatment and current medications. Dosage and frequency of omalizumab injections were dependant on each patient's weight and IgE level. Subcutaneous dosage of omalizumab ranged from 150 to 375 mg and was offered in either 2 or 4-week intervals. Categorical, explanatory variables were summarized by frequency and absolute proportion. Continuous, explanatory variables were summarized by mean, standard deviation and range. The primary outcome variables were change in SNOT-22, endoscopic mucosal scores and IgE levels evaluated before and after treatment. As the duration of treatment varied among patients included in this case series, the endoscopic score was averaged over each respective follow-up period. The outcome variables were recorded as continuous, numerical outcomes and summarized by mean and standard deviation. The number of injections received and months treated with omalizumab were also reported. Frequency of concurrent medication was recorded and compared to baseline levels as categorical outcome variables. These observations were reported by count and absolute proportion.

Please cite this article as: Gan EC, et al, Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate..., Am J Otolaryngol–Head and Neck Med and Surg (2015), http://dx.doi.org/10.1016/j.amjoto.2015.05.008

Table 1 – Subject demographics and baseline characteristics.

Characteristics	Mean (SD)/ frequency (%)
Age (years)	48.1 (11.8)
Sex	
Males	3 (43%)
Females	5 (57%)
Race	
Caucasian	5 (71%)
South Asian	2 (29%)
Forced expiratory volume (liters)	2.7 (0.3)
Number of sinus surgeries	
Mean	2.0 (1.5)
Range	1–5
Number of office-based polypectomies	
Mean	0.7 (0.8)
Range	0–2
Pre treatment immunoglobulin-E (IU/ml)	
Mean	238.1 (295.2)
Range	19–882

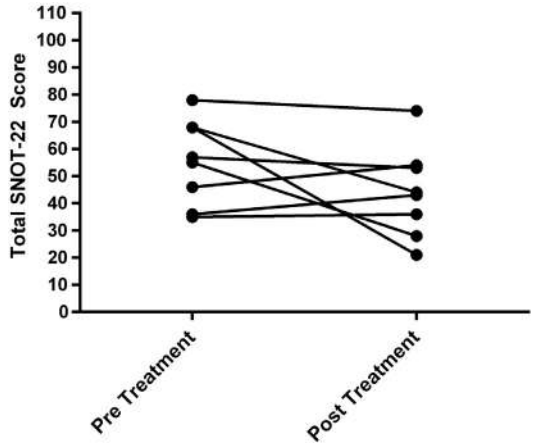


Fig. 2 – Comparison of SNOT-22 scores pre and post omalizumab therapy.

3. Results

A total of 8 patients received omalizumab, of which 1 patient (13%) did not continue treatment due to a significant reaction during initial administration. This patient had fever and dizziness immediately post injection. Symptoms resolved soon after, with no additional treatments or medication provided by the attending nursing staff. Omalizumab therapy was immediately discontinued and the symptoms did not recur. Excluding this patient from the review, this case series included 7 patients, consisting of 3 (43%) males and 4 (57%) females. The mean age of this cohort was 48.1 ± 11.8 years. All patients presented with moderate or severe asthma prior to receiving treatment of omalizumab, with a mean FEV_1 of 2.7 ± 0.3 liters. Patients had undergone on average, 2 ± 1.5 sinus surgeries (range: 1–5) and 0.7 ± 0.8 (range: 0–2) office-based polypectomies prior to receiving treatment. Pre omalizumab medications consisted of 7 (100%) patients self-administering topical budesonide, 3 (43%) received oral prednisone and 2 (29%) utilized oral itraconazole. Demographic data are summarized in Table 1.

Patients presented with a mean IgE-level of 238.1 ± 295.2 IU/ml (range: 19–882). An average of 12.3 ± 5.2 (range: 7–21) injections was administered, with mean follow-up time of 9.7 ± 2.9 (range: 7–14) months. The mean dose of omalizumab administered was 285.7 ± 57.5 mg (range: 200–375 mg). Among the study cohort, 5 (71%) patients receive injections every 4 weeks, whereas the remaining 2 (29%) patients receive injections at 2 week intervals.

The mean difference between pre and post SNOT-22 scores was 16.3 ± 17.1 (range: −1 to 47) points (31% improvement) (Fig. 2). Six of 7 (86%) of patients reported a reduction in sinus symptoms and subsequent improvement in quality of life post treatment. The mean difference in pre and post endoscopic scores was 22.0 ± 5.7 (range: 16–34 points), (61% improvement) (Fig. 3). The mean difference between pre and post IgE level was 60.9 ± 276.3 (range: −164 to 651 IU/mL) (Fig. 4). These observations were reported on average 7.9 ± 1.4 (range: 6–9) months post treatment. The use of concurrent medications was re-evaluated during the follow-up period. In regard to lung function, mean FEV1% predicted improved by 9.4 ± 1.2% (range: −6.6 to 14.9%, Fig. 5). Of all patients using budesonide prior to receiving omalizumab therapy (n = 7), 3 (43%) experienced a change in frequency and 1 (14%) discontinued use completely. Of those experiencing a change in frequency, 3 (75%) reduced their budesonide usage from twice daily to once daily. Of the three patients receiving oral prednisone prior omalizumab, all discontinued usage during the follow-up period. Similarly, the use of oral itraconazole was ceased in 1 of 2 (50%) patients after commencement of omalizumab injections. During this observational period, no patients were found to require subsequent office-based polypectomy or revision FESS after receiving omalizumab. The IgE levels post omalizumab therapy decreased significantly in two patients but were mostly slightly elevated in the remaining patients (Fig. 4).

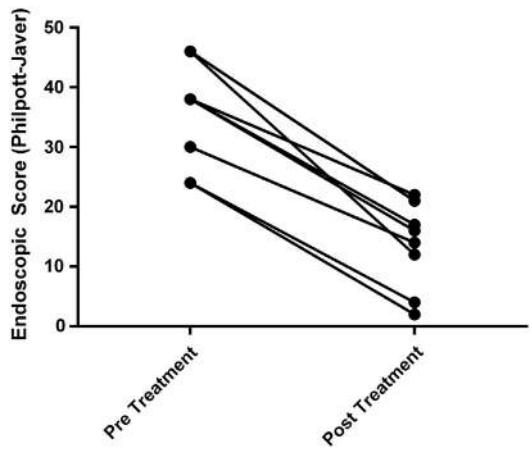


Fig. 3 – Comparison of endoscopic scores pre and post omalizumab therapy.

Please cite this article as: Gan EC, et al, Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate..., Am J Otolaryngol–Head and Neck Med and Surg (2015), http://dx.doi.org/10.1016/j.amjoto.2015.05.008

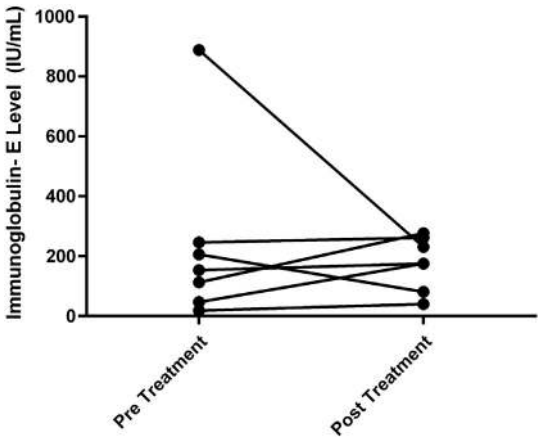


Fig. 4 – Comparison of medication usage pre and post omalizumab therapy.

4. Discussion

It has been reported that 70–88% of asthmatic patients experience sinonasal symptoms [25] and patients with CRSwNP are more likely to have concurrent asthma [26,27]. Although there are no available data in the literature on the prevalence of asthma in AFRS patients, most rhinologists would agree that a significant number of AFRS patients do suffer from asthma as well. Evans and Coop [28] first reported a positive effect of omalizumab on a patient with refractory AFRS in 2014. However, this study is believed to be the first reported case series in the English literature on the effects of omalizumab in post-FESS AFRS patients with moderate to severe asthma who have failed adjunct medical treatments. These medical treatments included topical (budesonide respules) and oral corticosteroids (prednisolone) and oral antifungal agent (itraconazole). Our study showed that patient symptom scores as well as endoscopic mucosal stage improved significantly after subcutaneous injections of omalizumab with a mean follow up period of 9.7 months.

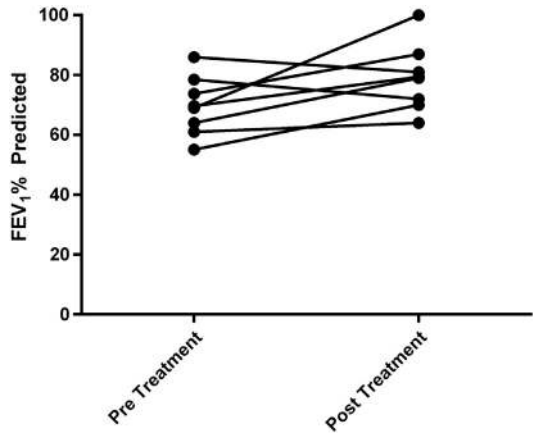


Fig. 5 – Comparison of immunoglobulin-E levels pre and post omalizumab therapy.

The clinical improvement seen in this study is in agreement with other studies demonstrating a favorable outcome in CRSwNP treated with omalizumab therapy [20,21]. In a small pilot study by Penn and Mikula among post FESS atopic asthma patients with CRSwNP treated with omalizumab, there was a significant reduction in the size of the polyps in the anti-IgE group compared to control [20]. In addition, they found that the severity of nasal polyposis correlated with total serum IgE levels in atopic asthmatics. In their study, omalizumab was administered by subcutaneous injection in 2- or 4-week intervals with a dose range of 150–375 mg (depending on patients' weight and pretreatment IgE levels) for an average of 5.5 months (range 3–8 months). In the only randomized double-blind placebo-controlled trial on omalizumab therapy on nasal polyps and asthma patients, Gevaert et al. demonstrated that there was significant improvement in total nasal endoscopic polyp scores, CT findings, airway symptoms and quality of life sores after 16 weeks of omalizumab treatment [21]. These improvements were seen irrespective of the presence of allergy.

Apart from reduction in symptom and endoscopic mucosal scores, omalizumab injections in our study reduced patient dependence on oral prednisolone and oral itraconazole, both of which are associated with potential significant side effects. All our patients were weaned off oral prednisolone therapy after commencement of omalizumab therapy. In a study of 19 CRSwNP patients with severe asthma treated with omalizumab, Vennera et al. demonstrated that there was a significant reduction in patient dependence on intranasal steroids (95% pre-treatment vs 42% post-treatment) and avoidance of revision surgery [13]. In their series, 13 patients (68%) had at least one endoscopic sinus surgery with a mean elapsed time of 29 months between surgery and commencement of omalizumab therapy. The IgE levels in our study were not reduced in all patients post omalizumab therapy. We hypothesize that the reason for this is because omalizumab binds to IgE without changing its physiologic production. Hence, the absolute levels would therefore not be expected to change.

Although the administration of omalizumab in patients with refractory AFRS and moderate or severe asthma appears to be a promising salvage therapy, there are several limitations to its use. The cost of omalizumab is approximately CAD three thousand dollars per subcutaneous injection. Fortunately, in our study, the cost of omalizumab was fully subsidized by the Canadian Healthcare System for eligible patients. Omalizumab is also administered subcutaneously on a 2-weekly or monthly basis. For the first injection, patients have to be observed in the clinic for three hours, in the presence of a physician with training in advanced cardiac life support (ACLS) and nurses who are trained in basic cardiac life support (BCLS). A fully equipped resuscitation trolley has to be readily available in the clinic. These measures are necessary to ensure that in the event of an anaphylactic reaction, the patient can be managed appropriately. An anaphylactic reaction post omalizumab therapy has not been reported in the literature. In our series, one patient developed a significant side effect (dizziness and fever) upon administration of subcutaneous omalizumab therapy which resolved with close monitoring. Finally, the optimal duration

Please cite this article as: Gan EC, et al, Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate..., Am J Otolaryngol–Head and Neck Med and Surg (2015), http://dx.doi.org/10.1016/j.amjoto.2015.05.008

and dosage of omalizumab therapy for the treatment of CRSwNP or AFRS have yet to be determined.

There were a few limitations in our study. First, the number of patients involved in this study was small. As the cost of omalizumab therapy is high and its use in Canada is approved mainly in patients with moderate or severe asthma, recruitment of a large number of patients will be difficult. Second, there was no control group in our study. However, these were post surgery AFRS patients who have already failed medical treatments available in our center. Third, many of these patients were on multiple concurrent medical treatments (topical and systemic steroid, oral itraconazole or nasal irrigations) while on omalizumab therapy although the dependence on these medications was reduced after omalizumab therapy.

5. Conclusion

Omalizumab therapy is a viable option in the treatment of patients with refractory AFRS and moderate or severe asthma. A well-designed large prospective randomized controlled trial to determine the effects and optimal dosage and duration of omalizumab therapy in patients with AFRS will be necessary.

Acknowledgments

We would like to sincerely thank Rachelle Dar Santos, BSc, CCRP, for her support and guidance in the process of obtaining ethics approval.

REFERENCES

[1] deShazo RD, Chapin K, Swain RE. Fungal sinusitis. N Engl J Med 1997;337:254–9.
[2] Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents. Otolaryngol Clin North Am 2000;33:419–33.
[3] deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. J Allergy Clin Immunol 1995;96:24–35.
[4] Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. Laryngoscope 2000;110:799–813.
[5] Manning SC, Holman M. Further evidence for allergic pathophysiology in allergic fungal sinusitis. Laryngoscope 1998;108:1485–96.
[6] Manning SC, Mabry RL, Schaefer SD, et al. Evidence of IgE-mediated hypersensitivity in allergic fungal sinusitis. Laryngoscope 1993;103:717–21.
[7] Panikou JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc 1999;74:877–84.
[8] Ryan MW. Allergic fungal rhinosinusitis. Otolaryngol Clin North Am 2011;44:697–710.
[9] Marple BF, Mabry RL. Allergic fungal sinusitis: learning from our failures. Am J Rhinol 2000;14:223–6.
[10] Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. Laryngoscope 2001;111:1006–19.
[11] Holgate S, Buhl R, Bousquet J, et al. The use of omalizumab in the treatment of severe allergic asthma: a clinical experience update. Respir Med 2009;103:1098–113.
[12] Casale T, Condemi J, LaForce C, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;286:2956–67.
[13] Vennera Mdel C, Picado C, Mullol J, et al. Efficacy of omalizumab in treatment of nasal polyps. Thorax 2011;66:824–5.
[14] Kanu A, Patel K. Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). Pediatr Pulmonol 2008;12:1249–51.
[15] Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. Pediatr Pulmonol 2008;243:607–10.
[16] Lebecque P, Leonard A, Pilette C. Omalizumab for the treatment of ABPA exacerbations in CF patients. Pediatr Pulmonol 2009;44:516.
[17] Sastre I, Bianco J, Mata HFG. A case of allergic bronchopulmonary aspergillosis treated with omalizumab. J Investig Allergol Clin Immunol 2012;22:145–7.
[18] Elmallah MK, Hendeles L, Hamilton RG, et al. Management of patients with cystic fibrosis and allergic bronchopulmonary aspergillosis using anti-immunoglobulin e therapy (omalizumab). J Pediatr Phamarcol Ther 2012;17:88–92.
[19] Tille-Leblond I, Germaud P, Leroyer C, et al. Allergic bronchopulmonary aspergillosis and omalizumab. Allergy 2011;66:1254–6.
[20] Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. Am J Rhinol 2007;21:428–32.
[21] Gevaert P, Van Zele T, Blomme K, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013;131:110–6.
[22] Presta LG, Lahr SJ, Shields RL, et al. Humanization of an antibody directed against IgE. J Immunol 1993;151:2623–32 [PubMed PMID:8360482].
[23] MacGlashan Jr DW, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438–45 [PubMed PMID:9013989].
[24] Philpott CM, Clark A, Javer AR. Allergic fungal rhinosinusitis—a new staging system. Rhinology 2011;49:318–23.
[25] Bresciani M, Paradis L, Des Roches A, et al. Rhinosinusitis in severe asthma. J Allergy Clin Immunol 2001;107:73–80 [PubMed PMID: 11149994].
[26] Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol 1999;28:717–22 [PubMed PMID:10480701].
[27] Johansson L, Akerlund A, Holmberg K, et al. Prevalence of nasal polyps in adults: the Skovde population-based study. Ann Otol Rhinol Laryngol 2003;112:625–9 [PubMed PMID:12903683].
[28] Evans II MO, Coop CA. Novel treatment of allergic fungal sinusitis using omalizumab. Allergy Rhinol 2014;5:172–4 [PubMed PMID:25565055].

Please cite this article as: Gan EC, et al, Omalizumab therapy for refractory allergic fungal rhinosinusitis patients with moderate..., Am J Otolaryngol–Head and Neck Med and Surg (2015), http://dx.doi.org/10.1016/j.amjoto.2015.05.008