original article

Anti-IgE therapy for asthma: an audit at a tertiary care centre in Saudi Arabia

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BACKGROUND: Although anti-IgE therapy has been shown to offer numerous benefits, we suspect it is underutilized locally. To date, there are no studies on any aspect of its use in the Arab region. There is also no information on whether physicians follow current guidelines nor on patient response to this form of therapy.

OBJECTIVE: Assess the use of omalizumab for patients with difficult asthma at a tertiary care center.

DESIGN: Retrospective, descriptive.

SETTING: Tertiary care hospital.

PATIENTS AND METHODS: Information was collected from medical records and interviews of all patients who received a minimum of 6 months of omalizumab, including data on practices of the prescribing physician (pulmonary versus allergy), indications, dose, subjective response, number of emergency room visits and hospitalizations, changes in asthma medications, adverse effects, and the setting for delivery of therapy.

MAIN OUTCOME MEASURES: Extent to which current guidelines for prescribing omalizumab were followed. Patient subjective and objective responses to treatment as reflected by changes in the use of medications and lung function before and after therapy.

SAMPLE SIZE: 50 patients.

RESULTS: Of the 50 consecutive patients, 35 were female and the mean (SD) age was 46.3 (9.2) years. Only 28 patients (56 %) met all the criteria for the prescription of omalizumab as per current guidelines; 18 (64%) by pulmonary and 10 (36%) by allergy physicians ($P<.05$). Pulmonary physicians performed more tests for conditions complicating or simulating asthma ($P<.05$). The mean (SD) duration of treatment by omalizumab of 35 (22) months was longer in patients managed by allergists (42 [24] months) than pulmonary physicians (30 [21] months) ($P>.05$). Both physician groups prescribed a lower initial dose than recommended ($P<.05$ recommended vs. prescribed). Patients reported a significant improvement in symptoms, reduction in the use of bronchodilators and oral steroids and in the use of healthcare services (from 16.28 [7.9] to 2.08 [1.78], $P<.0001$) mean values from sum of hospitalizations/year, ER visits/year, exacerbations/year, but not in other medications or pulmonary function tests ($P>.05$).

CONCLUSION: Despite several benefits, notably a reduction in utilization of health services and asthma medication, anti-IgE therapy is probably underutilized locally. Pulmonary physicians are more likely to follow the guidelines than allergy physicians. This study suggests that

there is room for improvement in the prescription practices, particularly in dosing and the setting for delivery. Further multicenter prospective studies are required to identify gaps in the current practices and improve asthma management.

LIMITATIONS: Too few patients met inclusion criteria, lack of control group, and use of a subjective assessment for patient symptoms as opposed to validated questionnaires.

CONFLICT OF INTEREST: None.

Asthma is a heterogeneous disease characterized by recurrent dyspnea, wheezing, cough and chest tightness and is usually associated with reversible airflow obstruction and airway hyperresponsiveness.[1] It affects an estimated 300 million people worldwide and is associated with significant mortality and morbidity. Treatment is based on the use of inhaled steroids and bronchodilator drugs. Although this approach is effective in the management of mild and moderate forms of the disease, patients with severe asthma may require oral steroids and other immunosuppressive regimens, which are associated with significant side effects.[2] In addition, people with poorly controlled asthma, despite conventional treatment, are at increased risk of hospitalization and emergency room visits.[3] Although this group accounts for a minority of patients with asthma (5%), it contributes to nearly 80% of the economic costs of asthma. Therefore, novel therapies are desperately needed for optimal management of this group of patients.[4]

It is estimated that more than 50% of people with poorly controlled asthma have allergic immunoglobulin E (IgE)-mediated asthma. Furthermore, over half of patients with asthma in the United States and other developed countries are atopic, with one or more positive skin tests to common allergens and detectable allergen-specific IgE concentrations in serum and therefore may benefit from treatments targeted at IgE.[5] Omalizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds IgE with high affinity that has been developed for the treatment of allergic diseases.[6,7] In 2014, a systematic review that included 25 randomized trials of patients with mostly moderate but also severe asthma receiving inhaled glucocorticoids, showed several benefits with the addition of omalizumab, including a reduction in the risk of exacerbation from 26 to 16 percent over 16 to 60 weeks of treatment, a reduction in the risk of hospitalization for asthma from 3 to 0.5 percent over 28 to 60 weeks, and a reduction in the dose of inhaled glucocorticoids.[4] Most of those studies involved patients with moderate asthma. Finally, the Global Initiative for Asthma (GINA) recommended omalizumab as an add-on therapy in step 5 for patients with severe asthma.[8] Similarly, the local Saudi Asthma Guidelines recommended omalizumab for step 4.[9] Despite proven efficacy, introduction of such drugs has been slow in developing countries. Omalizumab was registered in Saudi Arabia several years ago and was added to the formulary at King Faisal Specialist Hospital and Research Centre (KFSHRC) in 2007. However, to the best of our knowledge, there are no published studies on the use of this drug and on whether physicians in the Arab region are following the guidelines for its prescription. Therefore, this study was conducted to examine the prescription practices of this recently introduced medication at a tertiary care center in Saudi Arabia.

PATIENTS AND METHODS

A list of all patients receiving omalizumab (Xolair, Genentech, Inc. South San Francisco, California, US) was obtained from the pharmacy at KFSHRC. Information on the usage of omalizumab was collected by patient interview at the clinic or the day care unit. Additional information on baseline status prior to therapy was obtained retrospectively from medical, pharmacy and laboratory records of pulmonary function tests (PFT). Inclusion criteria included a physician's diagnosis of asthma that was made by either the respiratory or allergy consultant, and a prescription of omalizumab for a minimum of 6 months as verified from the pharmacy records. The study included all patients prescribed the medications since its introduction to the hospital (2007) until the end of 2016. The patient population of KFSHRC includes people from all regions of the country.

Information sought included: (1) results of tests performed for asthma and conditions associated with asthma or that simulate asthma before starting omalizumab, (2) physician's assessment of degree of asthma control and severity before and after treatment with

omalizumab, (3) information on how strictly the recommended guidelines[10] for prescribing omalizumab were followed (obtained from the patient charts). This included being more than 12 years of age, having moderate to severe persistent asthma, being symptomatic despite optimal therapy, and having undergone repeated (>3 times) use of health care services in the last 12 months due to asthma, total serum IgE level between 30 and 1500 international units/mL, positive skin or in vitro testing for allergen-specific IgE to allergens. Adverse effects of omalizumab, and patient feedback on the delivery setting of omalizumab was also noted.

This study was conducted in accordance with the national and international ethical standards and policies for conducting research on human subjects such as the Declaration of Helsinki. In addition, the study was approved by the Institutional Review Board and Office Of Research Affairs at KFSHRC. Signed consent was obtained from the patient for participation in the study.

Statistical analysis of data was done using the software package SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics for the continuous variables were reported as mean and standard deviation and categorical variables were summarized as frequencies and percentages. Continuous variables were compared by the independent t-test or ANOVA, while categorical variables were compared by the chi-square test. The level of significance was set at $P<.05$.

RESULTS

Only 50 patients met the inclusion criteria; 35 were female (70%), mean age was 46.3 (9.2) years, all were nonsmokers, and 41 patients (82%) had allergic rhinitis. Half of the patients were managed by pulmonary physicians and the other half by allergy physicians. Analysis of the testing practices showed that 9 of the 25 of patients managed by pulmonary physicians (36%) had full testing for conditions that can complicate or simulate asthma compared with 3/25 (12%) of those managed by allergy physicians ($P<.05$) (**Figure 1**). Twenty-eight patients (56%) had all the criteria for the prescription of omalizumab as per current guidelines: 18 of the 25 patients managed by pulmonary physicians (72%) compared with 10 of 25 (40%) managed by allergy physicians ($P<.05$). The mean (SD) duration of treatment by omalizumab of 35 (22) months was longer in patients managed by allergists (42 [24] months) than pulmonary physicians (30 [21] months) ($P>.05$). The initial dose of omalizumab for both pulmonary and allergy physicians was significantly lower than the recommended dose: 449 (150) mg/month compared with mean (SD) recom-

mended 738 (319) mg/month ($P<.05$).

Assessment of the clinical response as reported by patients showed a significant improvement in symptoms (n=46), reduction in emergency department visits (n=40), and hospitalizations (n=15), improvement in exercise (n=12), and sleep (n=7), and decrease in exacerbations (n=5). Review of medical records also showed a decrease in the utilization of health services from 16.28 before omalizumab to 2.08 after omalizumab. However, no significant improvement was seen in PFTs (**Table 1**). Review of medications use after omalizumab showed statistically significance decrease in the use of short-acting beta-agonists (SABA) and oral corticosteroids (OCTs), but no significant change in the use of long-acting beta-agonist (LABA), short acting anticholinergic drugs (SAACs), long acting anticholinergic drugs (LAACs), inhaled corticosteroids (ICS) and leukotriene-receptor antagonist (LTRA) (**Table 2**). Only 12 patients (24%) had minor adverse reactions, the most frequent being pruritus (reported by 6/50 pa-
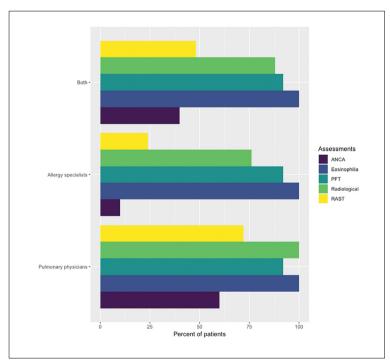

Figure 1. Use of tests for conditions that can complicate or simulate asthma by pulmonary physicians and allergy physicians. ANCA: anti-neutrophil cytoplasmic antibody tests to rule out eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), Eosinophilia: peripheral eosinophilia due to allergic bronchopulmonary aspergillosis (ABPA), PFT: pulmonary function tests for evidence of reversible obstruction and to rule out chronic obstructive lung disease, vocal cord dysfunction, Radiological: tests to rule out structural diseases of the lung (e.g. cystic fibrosis, bronchiectasis including ABPA, or endobronchial lesions, RAST: radioallergosorbent test for measuring human anti-Aspergillus fumigatus antibodies of the IgG class as part of ruling out ABPA.

Table 1. Changes in mean (variance) values pulmonary function tests after treatment with omalizumab.

	FVC%	FEV1%	FEV1/FVC	MMEF 75/25%
Before Omalizumab	74.8 (18.6)	60.8 (20.0)	68.4 (15.0)	29.0 (17.3)
After Omalizumab	76.0 (18.0)	61.6 (16.7)	68.8 (14.1)	30.7 (14.5)
P value	.4544	.6903	.3708	.4262

FVC: forced vital capacity, FEV: forced expiratory volume at end of first second of expiration, MMEF: maximal mid-expiratory flow.

Table 2. Changes in dose of other medications for asthma after treatment with omalizumab.

	SABA	LABA	SAACs	LAACs	ICS	OCTs	LTRA
Before Omalizumab	655.6 (386.5)	137 (83.3)	29 (42.9)	3.24 (6.9)	506.7 (131.1)	7.2 (5.7)	8.8 (3.2)
After Omalizumab	152.9 (203.2)	132.6 (85.5)	29 (50.5)	5.3 (8.12)	478.3 (167.3)	2.9 (4.2)	8.2 (3.8)
P value	<.001	>.05	>.05	>.05	>.05	<.001	>.05

SABA: short-acting beta-agonist; LABA: long acting beta-agonist; SAAC: short-acting anti-cholinergics; LAAC: Long-acting anti-cholinergics; ICS: inhaled corticosteroids (mcg/day); OCT: oral corticosteroids; LTRA: leukotriene receptor antagonists (mg/day).

tients). Others included fatigue (n=4), dizziness (n=1), and bronchospasm (n=1). Patients who received omalizumab at the day care unit (90%) were less satisfied than those who received it in their local hospitals (10%) because of the need to make travel arrangements and the long waiting time.

DISCUSSION

To our knowledge, this report is the first on the use of anti-IgE therapy for asthma in the Arab region. We believe that such lack of reports and the fact that only 50 patients could be found at our centre, where thousands of patients are managed, reflects underutilization. The reasons are probably multiple, including a reluctance to change to newer treatments, unfamiliarity, doubts on its efficacy, cost, or concern about adverse effects. It is hoped that this report will increase awareness of anti-IgE therapy, which is now approved in most guidelines,[8,9] and dispel some of these unfounded concerns. Recommendations to use anti-IgE therapy are based on many studies that have documented the positive clinical response to omalizumab. For example, Hanania et al[11] and Vignola et al (SOLAR study)[12] showed a decrease in the use of rescue medications after using omalizumab. Also, the INNOVATE study[13] reported a reduction in the use of health care services after omalizumab treatment for 28 weeks in 419 patients. Likewise, several observational studies

reported variable degrees of improvement in quality of life (QOL) with different measures including AQLA, Mini AQLA , EQ-5D index/utility and EQ-5D (VAS).[13-15] Not all patients, however, have a positive clinical response to omalizumab. Novelli et al performed a cross sectional study in 26 centers in Italy, the aim of which was to assess the level of asthma control after introducing omalizumab.[16] Despite the use of omalizumab for a considerable period of time, asthma in 25% of their patients was still poorly controlled.

Our observations are consistent with most of the published reports internationally; there was an improvement in asthma in our patients after treatment with omalizumab. This was reflected by the subjective symptomatic response, significant reduction in usage of healthcare services and the use of rescue medications and oral corticosteroids. There was no reduction in use of inhaled corticosteroids and no significant improvement in PFTs, but this is consistent with the literature, in which improvement in PFTs after omalizumab are reported as variable. While many studies[13,14,17-19] have reported significant improvement, both the INNOVATE study[13] and the EXALT study[17] showed that differences in lung functions (FEV1) were small in absolute terms (at 2.8% and 4.4%, respectively). Randolph and Kearney[20] did not show any change in PFTs after a relatively long duration of treatment (mean of 2.1 years), as was the case in our study.

As for how closely physicians follow the guidelines, we are not aware of studies that have addressed physician practices. In general, most physicians comply poorly with guidelines.[21,22] In our study, tests on patients who qualified for anti-IgE therapy were often incomplete. For example, the assessment of allergic sensitization either by (skin test or vitro testing) was frequently missed (28%). It is not clear why these tests are underused because they were available and are free of charge at our center. Similarly, although many diseases are associated with or complicate asthma (e.g. allergic bronchopulmonary aspergillosis and eosinophilic granulomatosis with polyangiitis),[23] diagnostic tests to rule out these diseases were often not uniformly performed.

The differences in prescription practices between pulmonary and allergy physicians may indicate that allergists felt more confident about use of anti-IgE therapy, thus not requiring all criteria for prescription. The duration of treatment suggests that the allergists started to use omalizumab earlier than pulmonary physicians. Pulmonary physicians were more meticulous, and performed tests to rule out asthma-like diseases.

Our study showed a significant difference between the dose prescribed by our physicians and the recommended dose. Appropriate dosing of omalizumab is a crucial component for the drug to achieve its effect. Treatment reduces serum free IgE concentrations in a dose-dependent manner. The clinical benefits with omalizumab in patients with asthma are observed when serum free IgE levels are reduced to <50 ng/mL (20.8 IU/mL).[23-25] The positive clinical response may have been greater had our physicians prescribed higher doses. The use of a lower dose follows previous guidelines in 2007, which have since evolved with increasing experience with the drug. An update on dosing for patients with high levels of IgE (based on body weight) was introduced in 2013.[26]

Omalizumab was shown to be well tolerated in many studies. Corren et al[27] studied the adverse reactions of omalizumab in a total of 2111 patients. The most frequently reported side effects were upper respiratory tract infection, headache, nasopharyngitis, sinusitis and local injection pain and pruritus. Our patients received omalizumab for relatively long periods of time (mean, 30 months; SD, 22 months) with only a few adverse reactions, none of which was life threatening. However, the setting for delivering omalizumab was not satisfactory for many patients, mainly because of the long waiting time before receiving the injection in the day care unit. As a result, we have switched to giving the injection in the clinic setting or providing the drug to patients to be given in their local hospitals. In addition, the pharmacy is planning to provide the drug preparation in the form of prefilled syringes, which is less time consuming.

To our knowledge, this study is the first in the region to assess the prescription practices of omalizumab among different specialties and assess the response of patients. However, the study is limited by the small number of patients and lack of a control group. The number of eligible patients was surprising considering that our center provides care to many patients with difficult asthma; this may reflect underutilization. Unfortunately, our study did not look into how many patients have the potential to benefit from anti-IgE therapy who were not prescribed the medication. Also, symptoms were assessed subjectively because validated questionnaires were not used routinely to monitor the patients. More research is needed to confirm our findings and address these issues.

In conclusion, although omalizumab offered several benefits, notably a reduction in utilization of health services and asthma medications, this audit suggests that there is still room for improvement, including wider use for eligible patients, better dosing based on current guidelines and changes in the delivery setting. The differences between pulmonary and allergy physicians in following the guidelines warrant exploration, as well as further analysis of differences in outcome of patients managed by each group. Further multicenter prospective collaborative studies are required to identify gaps in the current practices and improve asthma management.

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