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Research Article

Effectiveness of Omalizumab in Severe Asthma Inadequately Controlled with Standard Therapy

Md Sayedul Islam*

Department of Respiratory Medicine, National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka, Bangladesh

***Corresponding Author:** Md Sayedul Islam, Department of Respiratory Medicine, National Institute of Diseases of the Chest and Hospital, Mohakhali, Dhaka, Bangladesh.

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Abstract

Background: Omalizumab, a recombinant monoclonal anti-IgE antibody, has demonstrated efficacy in patients with moderate to severe persistent allergic asthma. Patients with severe persistent asthma despite GINA 2005 step 4 treatment are at risk for asthma-related morbidity and mortality. This study aimed to investigate the efficacy, safety and long term control of asthma after discontinuation of omalizumab. in a private Hospital.

Methods: This is a retrospective study carried out in a private Hospital from January 2010 to June 2016 for assessing the efficacy of omalizumab therapy over 4 months and 9 month and to see the changes in asthma medication, asthma control, frequency of exacerbations and hospitalization rate at baseline and after omalizumab discontinuation. Asthma patients (age 20 - 60 years) not controlled GINA 2005 classification step 4 treatment were selected and given injection omalizumab and followed up and compare the result of baseline and after 9 month of drug therapy.

Results: 31 patients were included in this studied for the effectiveness of omalizumab,, 20 female and 11 male, mean age 45.71 ± 21 years. There were no major adverse events from the study. Omalizumab significantly reduced the rate of clinically asthma exacerbations from 31.8%to 17.2% (P < .001) and all asthma-related emergency visits. There was a reduction in asthma medication post omalizumab therapy. It also improve the AQLQ score from 4.5 ± 1.7 to 5.9 ± 76 (P value < .05) and ACT score 11.17 ± 23 to 13.89 ± 12 (P value < .001). So the results shows significant improvement.

Conclusions: Patients receiving omalizumab therapy for 4 months and above were found to reduce the use of many asthma medications and also found less asthma exacerbation, ER visits, and hospitalization, even after the discontinuation of omalizumab. This study support that omalizumab is effective in patients with moderate to severe asthma.

Keywords: *Omalizumab; Asthma; Retrospective Study*

Introduction

Bronchial asthma is a chronic inflammatory disease of airway characterized by hyperresponsiveness of the trachea and bronchi to various stimuli manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy [1].

The most recent revised global estimate of asthma suggests that as many as 334 million people have asthma, and that the burden of disability is high [2]. About 7 million people in Bangladesh are suffering from asthma [3]. The unique guideline for the management and prevention of asthma adopted by Global Initiative of Asthma (GINA). Majority of the allergic and non-allergic asthma can be well controlled by ICS+ LABA combination with or without short course use of oral steroid [4]. Severe asthma is characterized by a difficulty to achieve disease control despite high-intensity treatment. Current estimates of the prevalence of severe asthma are between 5 and 10% of all asthma [5]. These group of patients remains uncontrol with standard step care management and needs frequent ER visit and hospi-

talization. Before the introduction of Omalizumab, moderate to severe cases of asthma, regardless of their allergic or non-allergic nature had been generally treated with corticosteroids and bronchodilators. GINA recently added Omalizumab as add-on therapy in step care management. Omalizumab received approval by the Food and Drug Administration (FDA) in 2003 for treating patients 12 years and older with moderate to severe allergic asthma [6]. It has also received approval in many other countries for treating patients 12 years and older with severe, persistent allergic asthma and available in our country since 2007.

Omalizumab is a recombinant humanized monoclonal antibody directed against IgE to inhibit the immune response to allergen exposure. This anti-IgE is directed against the binding site of IgE for the high-affinity receptor and as a result, prevents free-serum IgE from attaching to mast cells and other IgE receptor-expressing cells thus preventing IgE-mediated responses.

From the initial studies in patients with mild allergic asthma, omalizumab demonstrated clinical effects with inhibition of allergen-induced lung function changes in both the early- and late-phase bronchoconstrictor responses [7,8]. In patients with moderate-severe allergic asthma, omalizumab reduced asthma exacerbations and corticosteroid requirements [9-11].

Perhaps the most dramatic effect, which was not foreseen at the time when the anti-IgE therapy was designed and which was discovered during the clinical trials, is that as the free IgE in patients is depleted by omalizumab, the FcεRI receptors on basophils, mast cells, and dendritic cells are gradually down-regulated with somewhat different kinetics, rendering those cells much less sensitive to the stimulation by allergens [12-14].

Methods

Data sources

This is a retrospective data based study from the records of outpatient care in a private hospital in Dhaka Bangladesh. The data sheet includes basic demographics, diagnoses from specialist, details of the ER visit and hospitalization, detailed information on prescribed medications.

Study design

After diagnosis of asthma their severity was assessed before treatment. Patients who have poorly controlled asthma despite taking high-dose inhaled corticosteroids (ICSs) and long acting β2-agonists (LABAs) and GINA 2005 classification Step IV management were included. Baseline GINA classification 2005, the ACT scoring, and the AQLQ score, Serum IgE level and details of current medications were recorded.

Patients were counselled and oral consent taken for their management with injection Omalizumab as add-on therapy. All the patients were started on omalizumab injections every 4 weeks, regimen. It is administered by subcutaneous injections. Dose of omalizumab is calculated based on the patient's weight and baseline IgE serum level. The patients were followed up monthly but detailed assessment were done at week 16 after initiation of drug to decide whether they would continue with the treatment based on the scientific leaflet.

After the second detail visit occurred at week 16 the final visit occurred at week 36 and each time by completing a) the Juniper Asthma Quality of Life Questionnaire (AQLQ), b) the ACT scoring c) Changes of GINA classification. d) the number of exacerbations and specific use of health care services were recorded during the study and compared with the patient's history in the 12-month period before treatment. Another group of patients who were prescribed omalizumab due to presence of their indication as add-on therapy but did not received injection because of different reasons were also followed up. The results were compared with baseline for any clinically meaningful improvement after treatment initiation.

Result

The data including age, gender, Smoking history, and economic condition, educational status were recorded. In the treatment population (TP) majority 22 (70.96%) of patients were aged 40 to 60 years old and male female ratio was 5:3. 22 (70.96%) of patients were nonsmoker, only 9 (29.03%) of patients were ex-smoker.

Variables		TP-31	ITP-25	
Age	22 - 40 yrs	6 (19.35%)	5 (20%)	Mean age 45.71 ± 21
	41 - 60 yrs	22 (70.96%)	17 (68%)	
	> 60 yrs	3 (9.67%)	3 (12%)	
Sex	Male	20 (64.51%)	15 (60%)	M: F = 5:3
	female	11 (35.48%)	10 (40%)	
Weight	Mean body wt	57.9 ± 21.2	56.2 ± 21.1	
Smoking History	Current smoker	00	00	
	Ex-smoker	9 (29.03%)	7 (28%)	
	Non- smoker	22 (70.96%)	18 (72%)	
Economic condition		good	good	
Education		Higher	higher	

Table 1: *Baseline demographic variables (n = 31).*

TP: Treatment Population; ITP: Intended to Treatment Population.

Table 2 showed the physiological parameters related to asthma severity assessment both in treatment population and intended to treatment population. IgE level, AQLQ scoring, GINA 2005 classification leveling, and ACT scoring done at baseline for both group values shown in this table.

Variables	Range	TP (mean ± SD)	ITP (mean ± SD)
IgE	350 to > 2000	763 ± 14 IU/ml	740 ± 1.06 IU/ml
FEVI(% pred)	43- 76	65.8 ± 21	64.7 ± 1.98
AQLQ	overall	4.5 ± 1.7	4.5 ± 1.6
	symptoms	4.6 ± 1.4	4.6 ± 1.1
	Activity limitation	5.1 ± 1.3	4.9 ± 1.8
	Emotion function	4.2 ± 1.1	4.2 ± 1.3
	Envn. stimulation	4.0 ± 1.9	4.0 ± 1.2
GINA classification	Step III -- V	Step III-IV	Step III-IV
ACT score	19--8	11.17 ± 23	11.13 ± 15

Table 2: *Baseline Physiological variables*

IgE: Serum IgE level; FEV1: Force Expiratory Volume in First Second; AQLQ: Asthma Quality of Life Questionnaire; GINA: Global Initiative for Asthma; ACT; Asthma Control Test

Table 3 shows the parameters of poor control of asthma before starting Omalizumab in both groups that means treatment population (TP) and intended to treatment population. Here in combine 38 (67.85%) patients have daily day time symptoms, 37 (66.07%) patients have weekly nocturnal symptoms. Specialist visit were needed 38 (67.85%) patients and 22 (39.28%) have acute exacerbation. 100% needed ICS+LABA along with leukotriene receptor antagonist.

Variables	Frequency		TP-31	ITP-25	Total-56	%
Day time symptoms	< Once/week		4	4	8	8 (14.28%)
	> Once/week		4	6	10	10 (17.85%)
	Daily		23	15	38	38 (67.85%)
Night times symptoms	< 2 times/ month		3	3	6	6 (10.7%)
	> 2times/month		6	7	13	13 (23.21%)
	weekly		22	15	37	37 (66.07%)
Asthma health care visit	ER visit ≥ 1/ year		6	7	13	13 (23.21%)
	Specialist visit ≥ 1/year		23	15	38	38 (67.85%)
	Hospitalization ≥ 1/year		2	3	5	5 (8.92%)
Asthma exacerbation	≥ 1/year		13	9	22	22 (39.28%)
concomitant Medication	ICS+LABA		31	25	56	56 (100%)
	Oral steroid	Daily	5	4	9	9 (16.07%)
		Intermittent	26	21	47	47 (83%)
	Leukotriene antagonist		31	25	56	56 (100%)
	Anticholinergic		9	6	15	15 (26.78%)
	Theophylline/derivatives		28	21	49	49 (87.5%)

Table 3: *Indices of poor asthma control prior to Omalizumab.*

ER: Emergency Room; ICS+LABA: Inhale Corticosteroid+ Long Acting B2 Agonist

At 16 weeks of treatment GINA classification was revised. From the above table GINA classification of asthma changed significantly, thus frequency of daytime and nocturnal symptoms and FEV1 recorded were also changed significantly.

At 16 weeks ACT score was recorded. The ACT Score shown in the table 4 overall response to treatment was good as compared to group Intended to treatment. ACT score at baseline was 11.17 ± 23 which changes to 13.27 ± 11, which is statistically significant P < 0.001.

Population	N	Baseline	16 wks effective	P value
% improving in GINA classification				
ITP	25	Step III-IV	Step III/IV	NS
TP	31	Step III-IV	Step III	S
% improving in ACT Scoring				
ITP	25	11.13 ± 15	12.23 ±	NS
TP	31	11.17 ± 23	13.27 ± 11	P < .001
% improving in AQLQ score				
ITP	25	4.5 ± 1.6	4.5 ± 19	NS
TP	31	4.5 ± 1.7	5.2 ± 1.0	P < .05
Severe exacerbation free				
ITP	25	33.7%	31.9%	NS
TP	31	31.8%	19.5%	P < .001

Table 4: *At 16-weeks Omalizumab treatment effectiveness.*

TP: Treatment Population; ITP: Intended to Treatment Population; NS: Not Significant; S: Significant

Asthma related QoL was assessed at 16 week using Juniper asthma related QoL mini questionnaire (mini AQLQ). A change of ≥ 0.5 on the 7 points AQLQ represents a clinically meaningful improvement in asthma related AQLQ.

During Omalizumab treatment asthma exacerbation was also recorded. Severe exacerbation was defined as ER visit or hospitalization > 1 day with oral steroid > 20 mg/day; Non severe exacerbation was defined as oral steroid > 20 mg/day without ER visit or hospitalization.

At 36 weeks reassessment 12 patients discontinue the treatment after 16 weeks and only 19 patients completed 36 weeks treatment. These 19 patients were reassessed for parameter shown in the table 5 and found improvement in the GINA classification, ACT scoring, AQLQ scoring and severe exacerbation. At the end of follow-up, there was a reduction in all asthma medications compared to baseline and before the discontinuation of omalizumab. The doses of LABA/ICS, OCS, and SAMA also decreased post omalizumab therapy. There was a reduction in severe exacerbations or hospitalizations from baseline: 1 year before index day (31.2%, n = 31) to follow-up before discontinuation (11.8%, n = 19, p < 0.001).

Population	N	Baseline	36 wks effective	P value
% improving in GINA classification				
ITP	25	Step III-IV	Step III/IV	NS
TP	19	Step III-IV	Step III	S
% improving in ACT scoring				
ITP	25	11.13 ± 15	12.27 ± 11	NS
TP	19	11.17 ± 23	13.89 ± 90	< .001
% improving in AQLQ score				
ITP	25	4.5 ± 1.6	4.6 ± 23	NS
TP	19	4.5 ± 1.7	5.9 ± 76	P < .05
Severe exacerbation free				
ITP	25	33.7%	31.9%	NS
TP	19	31.8%	17.2%	P < .001

Table 5: *36-Weeks Omalizumab treatment effectiveness.*

TP: Treatment Population; ITP: Intended to Treatment Population; NS: Not Significant; S: Significant

Discussion

This study was carried out from January 2010 to June 2016 in a private general hospital to see the effectiveness of Omalizumab in moderate to severe asthma patients. The standard step care management in some percentage of severe asthma is not sufficient for well control even with short course of oral steroid. So some other means should be employed to treat these patients. Omalizumab is costly and not widely available drug and should be given in injectable form only. In these regard the efficacy of the drug must be studied vigorously, which inspire us for the study. Here we can see that the majority of patients with severe asthma between the age group of 41 - 60 years (70.96%) with mean age 45.71 ± 21 with M:F ratio 5:3 this result is consistent with other previous study. This study finding shows that the patients who received omalizumab therapy in a scheduled dose on the basis of serum IgE level and body weight for at least 16 weeks were found to have well asthma control in terms of reductions in asthma medications, exacerbation and related to other parameter even after discontinuation of drug.

Poorly controlled asthma patients with standard care therapy need repeated short course oral steroid and hospitalization due to exacerbation so this is an important parameter to see the effect of omalizumab. During Omalizumab treatment asthma exacerbation was also

recorded. Severe exacerbation was defined as ER visit or hospitalization > 1 day with oral steroid > 20 mg/day; Non severe exacerbation was defined as oral steroid > 20 mg/day without ER visit or hospitalization. In this study showed the significant reduction of exacerbation in Omalizumab group from31.8% to 17.2% (P value < 0.001) which was highly significant. This is important because patients are free from the side effect of steroid and relief from economic burden. The result of this parameter is consistent with that of Holgate., *et al*. [15] and a more recent study from Ireland [16] who showed that the reduction of exacerbation from 3.48 ± 2.20 to .93 ± 0.83.

Asthma control test (ACT) is a brief patients based assessment tool for control status of asthma. It assess asthma control over the past 4 weeks in a quantifiable manner. It consists of 5 questions that provide both the Physicians and patients, a quick and easy way to assess the level of asthma control. This test has been used in this study to see the effect of Omalizumab. Score > 25 means total control of asthma, score between 2o to 24 indicates well control, 10 to 19 not well control and score < 9 indicates chances of exacerbation asthma control test (ACT) score [17]. Nygaard L., *et al.* [18] used ACT to assess the clinical effect of Omalizumab in their study and they found that there is statistically significant increase in ACT score of 5.1 points [95% confidence interval (CI) 3.1 - 7.2, p = .0001]. Yang WH., *et al*. [19] also shows similar result where they found that overall ACT score at baseline was12.9 ± 4.49 and Omalizumab resulted in clinically meaningful changes from baseline (≥ 3 points). In our study there was significant improvement of ACT score from baseline 11.17 ± 23 to 13.89 ± 90 (P value < .001). This result is comparable to other study.

FEV1 is an important lung function parameter which is used to see the reversibility of airway and also for monitoring the treatment response. This has been taken as a vital parameter for the effectiveness for Omalizumab in this study. For the uncontrolled allergic asthma baseline FEV1 was taken and these were measured after 16 weeks and 36 weeks. Busse, Soler, Buhl., *et al*. [11,20,21] showed the significant improvement of FEV1 with treatment of Omalizumab. In this study also we have found the changes in the FEVI from baseline to final follow up 65.8 ± 21 to 70.34 ± 54 which is highly significant statistically (P value < .05) Our study is compatible with the findings from these studies in other countries, and it is the first short scale study our country.

Uncontrolled bronchial asthma patients have lower AQLQ due to decreased emotion, social and physical activity. AQLQ is an important parameter containing four domains consist of emotion, social, physical activity and environmental effect used in this study to see the effect of Omalizumab. Filling up and analyzing the Mini AQLQ questionnaire at baseline and after 16 weeks and 36 weeks were used to assess the changes. In this way an increase in overall score ≥ 0.5 points is significant improvement. In our study, improvements in AQLQ overall scores was clinically significant (≥ 1.4-points) in most of the patients compared with the ITP group. This result was comparable with the study done by Buhl., *et al*. [21] and meta-analyses done by Chipps., *et al*. and Niebauer., *et al* [22,23].

Omalizumab is given in subcutaneous route and the dose should be appropriately adjusted depending on Serum IgE and body weight because reducing the dose of omalizumab below that in the dosing table was not recommended, as the resulting increase in free IgE [21,23]? would cause deterioration in asthma control [24] which is revealed in The INNOVATE study (Investigation of Omalizumab in severe Asthma Treatment). In this study, patients treated with Omalizumab with at least 16 weeks duration, there were reductions in asthma medications, exacerbations and ER visits compared with baseline. Our study is compatible with the findings of cited different studies and it is the first short scale study our country. A larger study and longer follow-up period may be warranted in future.

Conclusions

Poorly controlled moderate to severe allergic asthma patients are prone to persistent symptoms, exacerbation and impaired quality of life. They also account for frequent use of oral corticosteroid which is associated diverse side effect. Omalizumab, the anti-IgE antibody used to treat these uncontrolled patients shows significant effectiveness. So Omalizumab reduces exacerbation, decreased asthma symptoms and asthma related hospitalization and also improved asthma quality of life. Omalizumab offers a new therapeutic option that can reduce the clinical and social asthma related burden.

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