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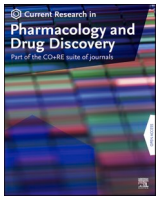

Real-world clinical utility (effectiveness) of omalizumab as add-on therapy in patient with difficult-to-treat severe allergic asthma

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A R T I C L E I N F O

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A B S T R A C T

Background: Severe allergic asthma (SAA) requires high-dose inhaled corticosteroids and additional medications. It poses a substantial health and financial burden. Omalizumab, an antibody that targets IgE, has improved symptoms and quality of life in severe allergic asthma (SAA) patients. Its impact in Bangladeshi patients is unknown, and this study aimed to evaluate its effectiveness in improving lung function in severe allergic asthma (SAA) patients.

Methods: This single-centre, real-world study aimed to assess omalizumab's effectiveness in 131 Bangladeshi patients with SAA. Information regarding demographics, BMI, and IgE levels, were collected from patients >12 years with poorly controlled SAA before and 3 months after omalizumab treatment. Pulmonary function tests (PFTs), including Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV1 %), FEV1/FVC (%), and Fractional Exhaled Nitric Oxide (FeNO), were performed according to established guidelines. A structured questionnaire was used for data collection. Ethical measures were taken in accordance with the current Declaration of Helsinki.

Results: The mean age of study population was 42.7 ± 16.15 (SD) years with majority being female (67.9 %). The mean BMI and IgE level was 28 ± 5.37 kg/m^2 and 594.3 ± 679.9 IU/mL respectively. The mean baseline FVC, FEV_1 and FEV_1/FVC ratio was 63.5 % ± 19.2, 61.3 % ± 21.8 and 80.4 % ± 12.6 respectively. The mean post-omalizumab FVC, FEV_1 and FEV_1/FVC ratio was 72.5 % ± 25.6, 68.3 % ± 28.2 and 79.1 % ± 13.8 respectively. The FeNO reading revealed that number of patients with <25 ppb reading increased post omalizumab treatment (70.2 % vs 84 %).FEV_1 expressed was significantly higher in patients post-omalizumab treatment than at the baseline ($p = 0.019$) and percentage of patients with FEV_1 below the predicted 50 % was higher at baseline compared to after omalizumab treatment (31.3 % vs 23.7 %). Similarly, the FVC was significantly higher post-omalizumab treatment compared to baseline ($p = 0.001$). The FEV_1/FVC ratio was not significantly different post omalizumab treatment ($p = 0.758$).

Conclusion: Our study finding have suggested that omalizumab as add on therapy achieved an adequate asthma control in patients with severe allergic asthma.

1. Introduction

In Bangladesh, 7 million people, including 4 million children, suffer from asthma-related symptoms, with the prevalence being approximately 7 % (Hassan et al., 2002). Severe asthma (SA) is characterized as asthma that necessitates high doses of inhaled corticosteroids in combination with at least one other controller medication, typically a long-acting beta agonist, as outlined in step 5 of the Global Initiative for Asthma (GINA). Alternatively, SA can be asthma that requires the use of systemic corticosteroids (SC) for more than 50 % of the previous year to prevent it from becoming 'uncontrolled,' or asthma that remains uncontrolled despite such therapy (Chung et al., 2014; Reddel et al., 2022).

SA affects about 4–11 % of the total population of asthma patients (Backman et al.; Hekking et al., 2015; Pakkasela et al., 2020). It is estimated that allergic sensitization, also known as the allergic phenotype, accounts for approximately 50 % of asthma cases, and this specific allergic phenotype is referred to as severe allergic asthma (SAA) (Pakkasela et al., 2020). Failing to effectively manage asthma can significantly affect clinical outcomes, quality of life, and healthcare resource utilization (Pavord et al., 2017; Bisgaard et al., 2012; Ortega

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et al., 2018; Arshad et al., 2014).

In those subjects who fail to respond to traditional asthma treatments, the addition of omalizumab (Xolair), a recombinant humanized monoclonal antibody which acts against IgE, to the asthma treatment regimen can be beneficial. IgE in asthma triggers inflammatory mediators, leading to bronchoconstriction, increased airway resistance, reduced ventilation, and decreased local oxygen levels, causing hypoxic pulmonary vasoconstriction and reduced lung perfusion. Omalizumab, by binding to and blocking IgE, can potentially disrupt this inflammatory process (Buhl et al., 2002; Finn et al., 2003). Studies and real-world evidence have shown that omalizumab effectively reduces asthma exacerbations, hospitalizations, and steroid use while improving symptoms, treatment effectiveness, lung function, and quality of life in moderate to severe allergic asthma (Djukanovic et al., 2004; Kelmenson et al., 2013; Paganin et al., 2017; Rubin et al., 2012; Siracká et al., 2023).

Despite significant advancements in the comprehension of omalizumab's mode of action, pharmacokinetics, efficacy, safety, and role in managing severe asthma, there is a dearth of information regarding its effectiveness in treating severe allergic asthma in Bangladesh. Although omalizumab was introduced in Bangladesh in 2009, there is a lack of real-time data on its efficacy in this context, therefore we sought to evaluate the real-world effectiveness of omalizumab as an add on therapy in difficult to treat severe allergic asthma patients of Bangladesh.

2. Method

2.1. Study design and subjects

This is an observational, single-center, real-world study aimed to evaluate the effectiveness of omalizumab in 131 patients diagnosed with SAA, who had received omalizumab in Bangladesh. The study collected retrospective and prospective information from subjects who had uncontrolled SAA and were >12 years.

Severe Asthma (SA) was defined based on the latest guidelines from the American Thoracic Society (ATS), European Respiratory Society (ERS), and Global Initiative for Asthma (GINA) as having a total IgE level greater than 30 IU/mL, along with a positive prick test or specific IgE level above 0.35 kU/L (Torres-Duque et al., 2022). Uncontrolled SA patients was defined as having one or more of the following criteria: (1) Poor symptom control: Asthma control questionnaire (ACQ) consistently >1.5 or Asthma Control Test (ACT) < 20 (or 'not well controlled" by GINA over the 3 months or evaluation); (2) Frequent severe exacerbations: 2 or more bursts of systemic corticosteroids (>3 days each) in the previous year; (3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year; (4) Airflow limitation: FEV_1 <80 % predicted (in the presence of reduced FEV1/FVC defined as less than the lower limit) following a withhold of both short- and long-acting bronchodilators (Chung et al., 2014).

Study eligibility criteria excluded subjects previously treated with omalizumab, subjects with a respiratory tract infection in the month prior to study start, severe hypersensitivity reaction to the medication, current smokers or subjects with a smoking history of >10 pack-years, subjects with severe co-morbidities, cancer and chemotherapy patients, immuno-comprised patients or subjects who were pregnant or lactating. All cases with uncontrolled SAA who received treatment between January 2022 (initiation of omalizumab implementation at the hospital) and September 2023 were included. Patients who missed their follow-up visits were excluded.

2.2. Study protocol

Patient who met the selection criteria were initiated treatment after they understood the side-side effects, potential complications and signed an informed consent. Before initiating omalizumab therapy, a comprehensive evaluation was conducted at baseline, encompassing of Pulmonary Function Test (PFT), demographic characteristics, Body Mass Index (BMI), Immunoglobulin E (IgE) levels, chest X-ray, sputum for Acid-fast bacillus (AFB) testing, Complete Blood Count (CBC), and vitamin D levels for each patient. Subsequently, subjects underwent a follow-up assessment three months after receiving the omalizumab treatment. At each assessment, pulmonary function test (PFT) was performed following American Thoracic Society/European Respiratory Society guidelines (Laszlo, 2006). Lung function parameters were determined in all patients at baseline and at 3 months after omalizumab therapy. Forced vital capacity (FVC), Forced expiratory volume in 1 s (FEV1 %), FEV1/FVC(%) and Fractional exhaled nitric oxide (FeNo) were expressed as percentages of predicted values (Quanjer et al., 1993). All the information was collected in a structured questionnaire.

2.3. Treatment protocol and monitoring

The dose of omalizumab prescribed by the physician was determined according to the package insert, based on body weight and total IgE level (Table-1). Omalizumab injection was administered subcutaneously. This was done at the clinic of the Department of Respiratory medicine by a trained registered nurse. Omalizumab was subcutaneously administered every 4 weeks (3 doses in 3 months), depending on the prescribed dosage. Following the initial dose, patients were monitored for 2 h in the clinic to observe for any signs of anaphylaxis. If the patient tolerated the medication well, on the next administration the patient required an observation period of 45 min. All patients received a stat dose of hydrocortisone as a safety precaution to avoid for a possibility of delayed reaction (Bousquet et al., 2011), by consultant herself, from the department of respiratory medicine.

2.4. Study endpoints

The primary study endpoint was the change in forced expiratory volume in 1 s (FEV1 %) at baseline and after 3 months of treating with omalizumab. Secondary endpoints were the change in FVC, FEV1/FVC and FeNo predicted while at baseline and 3 months after receiving omalizumab. All necessary information was recorded in a structured questionnaire.

2.5. Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies, and quantitative variables as measurements of central tendency and dispersion, according to the Shapiro Wilk's normality test. Categorical outcome measures were compared using the χ^2 test; continuous outcome measures, using Student's tests for paired data and pvalues $\leq$0.05 were considered significant. Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, Illinois, USA).

The study was approved by the ethical review committee of Public Health Foundation, Bangladesh (PHFBD) (PHFBD-ERC-SP07/2024). Informed signed consent was obtained from all eligible participant who agreed to participate. The authors declare no human subjects were harmed and all procedures were conducted in compliance with the STROBE guidelines, adhering to the ethical standards and regulations set forth by the Helsinki Declaration of the World Medical Association.

3. Results

3.1. Baseline clinical and biological characteristics of the study population

Mean age of the studied patients was 42.7 ± 16.15 (SD) years with a majority in 41–60 years (43.5 %). Among them, female patients were 67.9 % (n = 89) and male patients were 32.1 % (n = 42). The mean BMI was 28 ± 5.37 kg/m^2 and 31.3 % were obese. The mean serum IgE level

Table 1
Dosing table of omalizumab administration every 4 weeks according to body weight and IgE levels.

Pre-treatment serum IgE level(IU/ML)	Body weight (kg)			
	30-60	**>60-70**	**>70-90**	**>90-150**
≥ 30-100	150	150	150	300
>100-200	300	300	300	225
>200-300	300	225	225	300
>300-400	225	225	300	
>400-500	300	300	375	
>500-600	300	375	Do not dose	
>600-700	375			

**Doses >150 mg should be divided over more than one injection site (eg, 225 mg or 300 mg administered as two injections, 375 mg administered as three injections). Injections may take 5-10 s to administer (solution is slightly viscous).*

was 594.3 ± 679.9 IU/mL (table-2).

3.2. Outcome measures before and after omalizumab treatment

Baseline lung function parameters are detailed in Table 3. The mean baseline FVC, FEV_1 and FEV_1/FVC ratio was 63.5 % ± 19.2, 61.3 % ± 21.8 and 80.4 % ± 12.6 respectively. The mean post-omalizumab FVC, FEV_1 and FEV_1/FVC ratio was 72.5 % ± 25.6, 68.3 % ± 28.2 and 79.1 % ± 13.8 respectively. FEV_1 expressed as percentage of predicted values was significantly higher in

patients post-omalizumab treatment than at the baseline (p = 0.019). As a consequence, the percentage of patients with FEV_1 below the predicted 50 % was higher at baseline compared to after omalizumab treatment (31.3 % vs 23.7 %). Similarly, the FVC was significantly higher post-omalizumab treatment compared to baseline (p = 0.001). The FEV_1/FVC ratio was not significantly different post omalizumab treatment (p = 0.758) and the percentage of patients with FEV_1/FVC below 70 after omalizumab treatment was 20.6 % (table-2). The FeNO reading revealed that number of patients with <25 ppb reading increased post omalizumab treatment (70.2 % vs 84 %) and >50 ppb reading decreased post omaizumab treatment (4.6 % vs 3.1 %). Over all, it was reported that FeNO level reduced post-omalizumab treatment (Fig. 1).

Table 2
Baseline clinical and biological characteristics of the study population(n = 131).

	Frequency	Percentage
	n	(%)
Age (in years)		
<20	9	6.9
20–40	49	37.4
41–60	57	43.5
>60	3	10
Range (min-max)	12–89	
Mean ± SD	42.7 ± 16.15	
Gender		
Male	42	32.1
Female	89	67.9
Body mass index (kg/m^2)		
Mean ± SD	28 ± 5.37	
Obesity (n,%)	41	31.3
Serum IgE(IU/mL)		
Mean ± SD	594.3 ± 679.9	

Table 3
Outcome measures before and after omalizumab treatment (n = 131).

	Baseline	Post-omalizumab treatment	p-value[a]
Pulmonary function (%)			
FVC			
Mean ± SD	63.5 ± 19.2	72.5 ± 25.6	0.001
FEV_1			
Mean ± SD	61.3 ± 21.8	68.3 ± 28.2	0.019
Patients with FEV_1<50 % (n, %)	41(31.3)	31(23.7)	0.756[b]
FEV_1/FVC ratio			
Mean ± SD	80.4 ± 12.6	79.1 ± 13.8	0.422
Patients with FEV1/FVC ratio <70 (n,%)	22 (16.8)	27(20.6)	0.758[b]

Abbreviations: FEV_1=Forced Expiratory Volume in 1 s, FVC=Forced Vital Capacity, FEV_1/FVC ratio = Forced Expiratory Volume in 1 s/Forced Vital Capacity ratio.
[a] p-value obtained by paired *t*-test.
[b] p-value obtained by chi-square test.

4. Discussion

To the best of our knowledge, this is the first real-life study addressing the response of SAA patients older than 12 years in Bangladesh, to omalizumab as an add-on therapy to treat SAA. Our study showed that omalizumab was associated with a significant improvement in asthma control and pulmonary function (FEV_1, FVC, FEV_1/FVC ratio).

Patients with severe allergic asthma often experience a significant decline in lung function. In our study, FEV_1 expressed as percentage of predicted values was significantly higher in

patients post-omalizumab treatment than at the baseline (p = 0.019). As a consequence, the percentage of patients with FEV_1 below the predicted 50 % was higher at baseline compared to after omalizumab

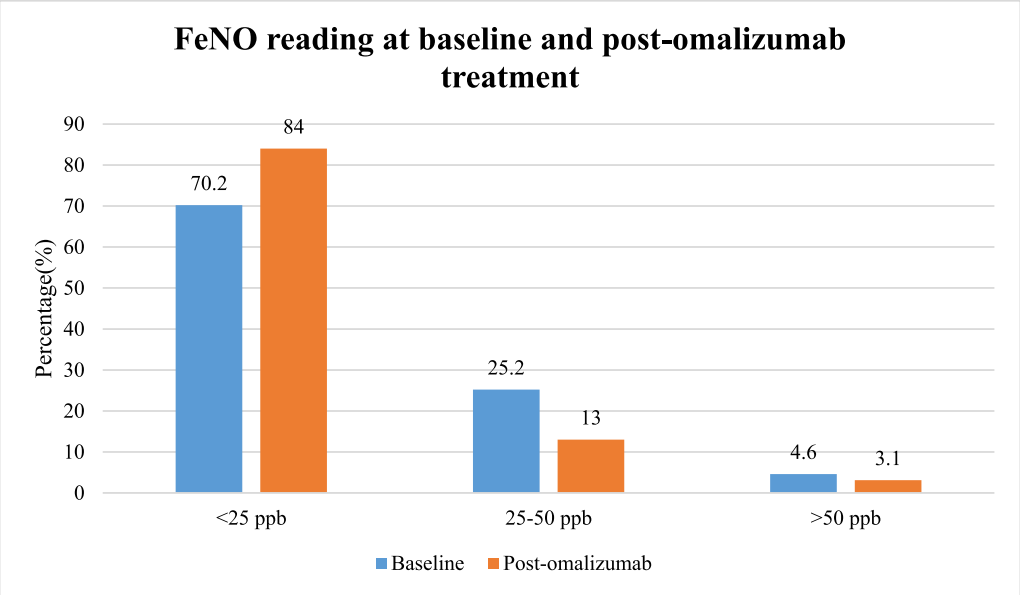

Fig. 1. FeNO reading at baseline and post-omalizumab treatment (n = 131).

treatment (31.3 % vs 23.7 %) which was consistent to the findings reported inrandomized controlled trials, where significant FEV_1 improvements have been reported in asthma patients treated with omalizumab (Humbert et al., 2005; Busse et al., 2007). Busse et al. found a mean FEV_1 increased from 68.2 % at baseline to 72.5 % of predicted value at 6 months in the omalizumab group, and from 67.7 % to 69.1 % of predicted value in the placebo group (Busse et al., 2007). The difference between groups was statistically significant. Moreover, in the trial carried out by Humbert et al., FEV (% predicted) was significantly better with omalizumab than with a placebo, with a difference of 2.8 % of predicted values (Corren et al., 2017).

We do acknowledge that patients receiving omalizumab within our healthcare system underwent rigorous monitoring, which could have potentially improved and enhanced the adherence to other pharmacological interventions and non-pharmacological measures. Although it is not possible to measure this effect in our study and it is possible that this influences the results, it is clear that the administration of omalizumab in patients with SAA in our health care facility have produced a benefit at least similar or greater than that described in randomized and real-life studies conducted with omalizumab (Corren et al., 2017).

Moreover, our study also depicted that the FVC was significantly improvement post-omalizumab treatment compared to baseline ($p = 0.001$) and the percentage of patients with FEV_1/FVC below 70 after omalizumab treatment was reduced. Our findings were similar to a real-life longitudinal study which demonstrated FEV1 and FVC improvement after omalizumab treatment at 4 months (Tzortzaki et al., 2012). Molimard et al. (2008) was the first to demonstrate a similar omalizumab benefit to that observed in clinical trials, in a historic-prospective "real-life" study of severe asthma patients treated with omalizumab with follow-up data at 5 months or longer.

Over all, it was reported that FeNO level reduced post-omalizumab treatment. The majority of studies showed that omalizumab therapy led to a significant reduction of FeNO levels both in adults (Mansur et al., 2017; Bhutani et al., 2017; Cabrejos et al., 2020; Zietkowski et al., 2010) and in children with severe allergic asthma (Silkoff et al., 2004). These results were also confirmed by Frix et al., who reported a significant reduction of FeNO after just 16 weeks of exposure to omalizumab. Interestingly, the decrease of FeNO levels appeared to be progressive throughout the follow-up of five years, reaching a median reduction of 15.3 ppb (Frix et al., 2020). However, other studies failed to show significant variations of FeNO during omalizumab treatment. In a small study by Johansson et al., no differences were found after 16 weeks of treatment, even though a nearby significant reduction of FeNO was observed in the subgroup with allergen-driven hyperactivated basophils (Johansson et al., 2018). Ledford et al. showed that there were no statistically significant differences between treatment groups with omalizumab at weeks 12, 24, 36, and 52, as measured by the change from baseline in FeNO values (Ledford et al., 2017). Study have shown that omalizumab can significantly reduce the production of nitric oxide (NO) by inhibiting the IL-4 pathway (Huang et al., 2005). However, the impact of omalizumab on IL-13 expression is less consistent (Holgate et al., 2009; Noga et al., 2003). A study by Sellitto et al. looked at non-asthmatic patients with chronic spontaneous urticaria and found that omalizumab reduced IL-4 levels but not IL-13. This suggests that changes in IL-13 during anti-IgE treatment might be due to the suppression of other inflammatory pathways rather than a direct effect of the drug (Sellitto et al., 2017).

The study's strength lies in its extended treatment period (>4 months), which provided ample time to demonstrate a positive response to omalizumab in patients with severe allergic asthma (SAA). Furthermore, it collected data in a clinical setting without any interventions, thereby reflecting the progress of patients who were not specifically chosen or treated in accordance with national and international asthma guidelines. Nonetheless, this study also had some inherent limitations. As a real-world observational study, the findings may be influenced by selection bias and confounding, leading to potential misinterpretation of omalizumab's effectiveness and limiting their generalizability. Additionally, the study did not assess adverse outcomes or factors contributing to lung function improvement. To establish a more definitive causal relationship, a randomized controlled trial with an adequate sample size is needed for a more comprehensive understanding of omalizumab's effectiveness and safety in this population.

5. Conclusion

In a real-life setting in Bangladesh, administering omalizumab for severe allergic asthma substantially led to better control of the condition. Our research found that omalizumab significantly improved both asthma management and lung function (FEV1, FVC, FEV1/FVC ratio). Further studies are required in Bangladesh to investigate how the phenotypic traits of severe allergic asthma might relate to the cost-effectiveness of omalizumab within our healthcare system.

Ethics approval and consent to participate

The study was approved by the Ethical Review Committee of Public Health Foundation, Bangladesh (**PHFBD-ERC-SP07/2024**). Informed written consent was obtained from all eligible participant who agreed to participate. The authors declare no human subjects were harmed and the procedures followed were in accordance with the ethical standards and regulations established by the Helsinki Declaration of the World Medical Association.

Availability of data and materials

Patient-level data will be available on request from the corresponding author.

Author contributions

All authors read and approved the final version of the manuscript, Conceptualization: RJ, SAA, ZH, Formal analysis: RJ, ZH, Investigation: RJ, SAA, ZH, Methodology: RJ, SAA, Resources: RJ, ZH, Supervision: RJ, SAA, ZH, Writing: RJ, SAA.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (version 3.0) in order to improve the readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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