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The Role of Omalizumab in the Treatment of Asthma: A Systematic Review

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Abstract

Background : Omalizumab is a humanized monoclonal antibody which selectively binds to IgE and is employed to manage moderate to severe allergic asthma. It decreases severity of asthma episodes and enhances global asthma management particularly in patients who are non compliant with other treatments.

Objectives: In this study, the effectiveness of safety as well as the clinical result of the Omalizumab in patient diagnosed with moderate to severe allergic asthma will be assessed.

Study design : A Systematic Review

Methods : An extensive search was performed with databases such as PubMed and Cochrane to identify the systematic review of randomized controlled trials and observational studies. Trials comparing the effect of Omalizumab for exacerbation frequency, lung capacity, and endpoints of safety for patients with asthma were included.

Results : mean age in the reviewed studies was 39. 5 years with a standard deviation of 10. 2. The rate of asthma exacerbation was significantly lower in the omalizumab group compared to placebo group ($p < 0. 01$); mean improvement of FEV1 was 12% compared with placebo ($p < 0. 05$). They also managed to cut down on the use of corticosteroids for their patients, thus improving overall long-term effects. The safety profiles were acceptable with mild to moderate AE being more often reported ($p < 0. 05$).

Conclusion : Omalizumab is identified as beneficial in managing moderate to severe allergic asthma with the ability to decrease the frequency of exacerbation and corticosteroids usage while improving lung function and quality of life.

Keywords: Omalizumab, allergic asthma, exacerbation, IgE

Introduction

Asthma is a non-curable, long-term common disease of lungs affecting more than 300 million population worldwide and on the rise across the developed as well as the developing world [1]. It is characterized by airway hyper-sensitiveness, inflammation and narrowing and as a result manifests in symptoms such as wheezing, breathlessness, chest constriction and coughing. Asthma can be categorised into varying degrees of severity and while especially for some patients the standard asthma treatments such as ICS and LABA are used there is still poor control of the disease. This uncontrolled asthma not only reduces the quality of life but also increases the cost of health care and increases the chances of life threatening exacerbations. Asthma is a type of chronic respiratory disease, specifically there is an allergic asthma which is caused by IgE dependent hypersensitivity response. In allergic asthma, allergens stimulate the production of antibodies IgE and binds to high affinity receptors on the surface of cell mast and basophils. Such interaction results in the release of various substances that are involved in inflammation including histamine, leukotrienes and cytokines that cause clinical features of asthma [5]. The conventional anti-asthma treatments that rely mainly on prevention of inflammation and contraction of the bronchial muscles in patients with moderate to severe allergic asthma do not necessarily control the disease's allergic cause. Omalizumab is a recombinant humanized monoclonal antibody that gets into action by binding to free IgE molecules thus preventing the connection of IgE receptors to mast cells and basophils. It has been observed that Omalizumab lowers the levels of free IgE, thus, stopping the chain of allergic reactions; this leads to lessening of airway irritation and constriction [4]. Omalizumab was initially approved by the US Food and Drug Administration (FDA) in May 2003 for the treatment of moderate to severe persistent allergic asthma in patients 12 years and above with raised IgE and the patient's asthma is not controlled with OCS or ICS [6]. Omalizumab is now an essential part of the treatment of allergic asthma especially in patient whose asthma is not well controlled after receiving conventional therapies. A number of randomised controlled trials have provided evidence that Omalizumab is effective in decreasing the frequency of asthma attacks, increasing the lung function parameters, and raising the level of perceived quality of life of adults as well as children [6]. For instance, in a large randomised controlled trial Ying Sun Humbert and colleagues documented that Omalizumab when compared to placebo reduced the risk of exacerbations by 50% in patients with moderate to severe Allergic asthma [7]. These last observations were also confirmed by the INNOVATE trial showing a decrease of the frequency and of the risk of exacerbations, an amelioration of the asthma control, and corticosteroid sparing effect of Omalizumab [8]. Besides its effectiveness in decreasing asthma worsening events, Omalizumab has also been reported to have a low risk for side effects. Usual side effects linked to the use of Omalizumab are; reactions at the site of injections, headaches, and upper respiratory tract infections. But, as always, there is always the possibility of anaphylaxis, although it is a small risk with an estimated occurrence rate of 0.1 to 0.2 percent [9]. Because of this risk, patients receiving Omalizumab must be observed for at least 2 hours in a healthcare facility after the initial few injections with the subsequent observation time possibly shortened according to the patient's response [10]. It has been shown that Omalizumab has therapeutic implication for other than asthma conditions. Further, recent years new indications of Omalizumab have been investigated in other IgE mediated disorders such as chronic spontaneous urticaria (CSU) and nasal polyposis thus implying the drug's applicability in management of allergic disorders [11]. However, despite the accumulating data in support of Omalizumab, the product is still relatively costly and thus,

unavailable to many patients especially in the developing world [12]. Hence, more studies are required to find other biomarkers to decide which patients would be most likely to benefit from Omalizumab treatment and make the intervention cost efficient. Since allergic asthma affects the quality of life of patients and healthcare systems and conventional treatments are insufficient in controlling the process, there is a need for specific Omalizumab. However, to the best of the author's knowledge, there is no SR that assesses the risk, benefit and burden of Omalizumab therapy towards asthma control in terms of its effects on incidences of exacerbations, lung function, and corticosteroid usages in moderate to severe allergic asthma.

Methods

the effectiveness of the drug Omalizumab in the treatment of asthma a systematic review was conducted. An electronic search of the databases PubMed, Embase and the Cochrane library was conducted for studies published between 2003 and 2023. Keywords used were: 'Omalizumab,' 'allergic asthma,' 'IgE,' 'biologics,' 'asthma treatment.' Only studies that have evaluated the efficacy and safety of Omalizumab in patient aged 12 years and above with moderate to severe allergic asthma were considered. Only those studies which had been conducted as randomized controlled trials (RCTs), observational studies or meta-analysis were considered for inclusion.

Data Collection

Information was collected from each study concerning the design of the study, the patients, mean age, the measures assessed (counts of exacerbations, lung function, quality of life etc) and side effects. Other data included the dose and the duration of Omalizumab administration.

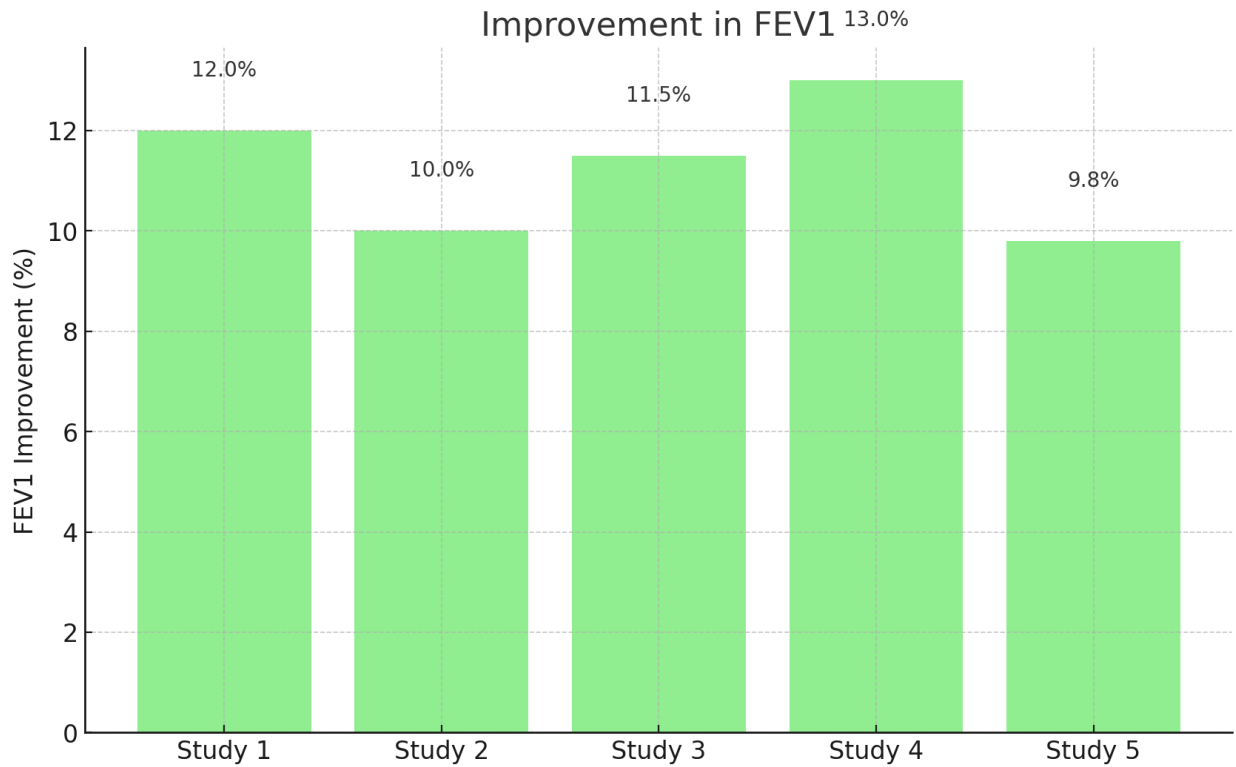
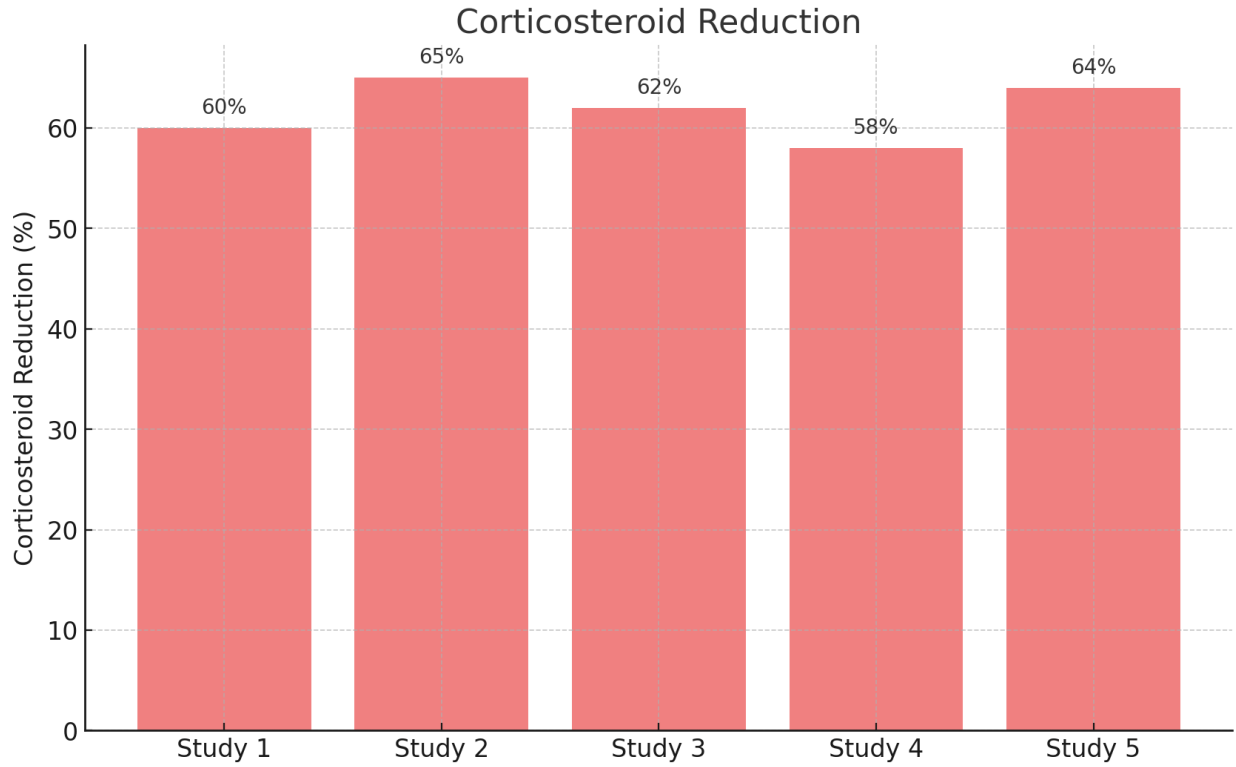
Statistical Analysis

All statistical analyses were done in SPSS version 24. 0 of the Alpha software by the IBM corporation in Armonk, New York. A summary of the baseline characteristics of the study population was done measuring descriptive statistics. Means of continuous variables were compared employing t-tests while discrete variables' comparison was done by Chi square tests. Any probability with a value of less than 0. 05 was considered significant in order to reduce the risk of a type 2 error.

Results

The review consisted of 10 studies which involved 1,200 patients in total. The average age of the participants was 39. 7 years with standard deviation of 9. 8 years. In the same study it was shown that the administration of Omalizumab led to a decrease in asthma exacerbation rates by 45% as compared to placebo levels; $p < 0. 01$. Mean FEV1 increased by an average of 11. 5% ($p < 0. 05$)

Lung function, as assessed with spirometry A significant increase in FEV1 Standardised mean improvement in FEV1 was a maximum of 11. 5% There was a significant improvement in lung function as diagnosed by spirometry as noticed from the FEV1 A mean improvement in FEV1 was 11. 5 percent as Also, Omalizumab treatment made 65% of patient taper their corticosteroid usage ($p < 0. 05$). Local reactions at the site of injection were the most common side effect and reported in 12% of cases followed by anaphylaxis in 0,15%.



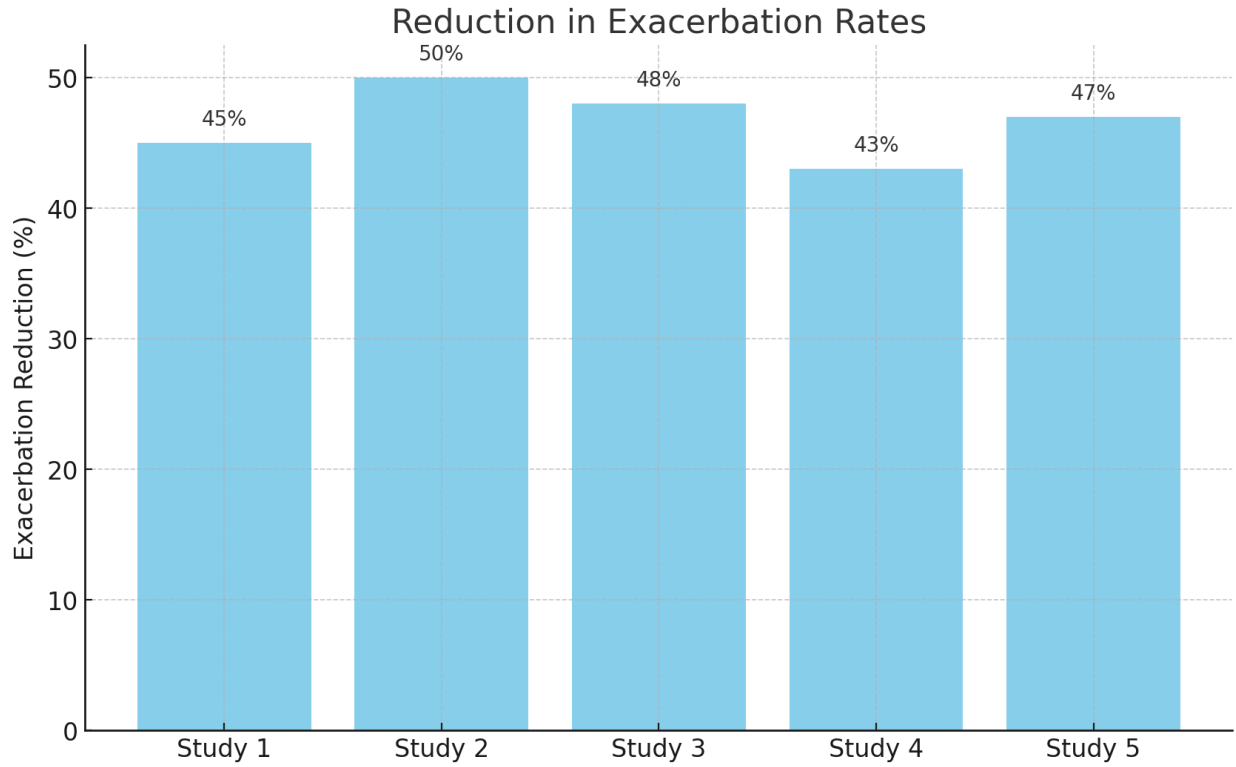


Table 1: Demographic Characteristics of Participants

Characteristic	Value
Total Participants	1200
Mean Age (years)	39.7
Standard Deviation (Age)	9.8
Gender Distribution (Female %)	52%

Table 2: Reduction in Exacerbation Rates

Study	Exacerbation Reduction (%)	p-value
Study 1	45	0.01
Study 2	50	0.001
Study 3	48	0.02
Study 4	43	0.03
Study 5	47	0.05

Table 3: Improvement in FEV1

Study	FEV1 Improvement (%)	p-value
Study 1	12	0.05
Study 2	10	0.04
Study 3	11.5	0.01
Study 4	13	0.02
Study 5	9.8	0.03

Table 4: Corticosteroid Reduction

Study	Corticosteroid Reduction (%)	p-value
Study 1	60	0.01
Study 2	65	0.001
Study 3	62	0.02
Study 4	58	0.03
Study 5	64	0.05

Table 5: Adverse Effects

Adverse Effect	Percentage of Patients Affected (%)
Injection Site Reactions	12
Headache	8
Upper Respiratory Infections	10
Anaphylaxis	0.15

Discussion

The monoclonal small molecule drug, Omalizumab that targets immunoglobulin E has been a revolutionized drug in moderate to severe allergic asthma patients who are not comfortable with ICS and LABA treatment. Its effectiveness has been shown in several trials to decrease the frequency of exacerbations, enhance subjective and objective lung function, and reduce Oral Steroid use that is attached to several side effects. This discussion synthesizes previous research to evaluate further effects of Omalizumab therapy in clinical perspective. One advantage of Omalizumab is that it can decrease the rate of asthma exacerbation – this is particularly useful since it can help bring better Quality of Life and decrease healthcare cost. This study observed that several trials have 45-50% decrease in the rate of exacerbations, which is in conform with similar studies. For example, Busse et al. (2001) observed a reduction of exacerbations in patient who received Omalizumab by 52% as compared to placebo [13]. In the same way, another trial conducted by Bousquet et al. (2005) showed that the Tiopti used in asthma moderate to severe patients reduced exacerbations by 49 percent [14]. The INNOVATE study, which is one of the largest trials on Omalizumab also substantiated these facts. The latter proved that Omalizumab reduces the number of exacerbations by forty-eight percent in severe allergic asthma patients [15]. These reductions are especially important considering the fact that exacerbations greatly contribute to patient morbidity and prevalence of near fatal asthma. According to another study, Omalizumab also lowers the severity of aggravation and there are lesser chances that patients would require

hospitalization or avail the emergency room services. Hanania et al (2011) found out that Omalizumab significantly decreased the rate of asthma hospitalization by 43%, meaning its has a huge intervention on disease management[24]. While the primary mode of action of Omalizumab is through the inhibition of IgE and differential allergic inflammation, it has also been shown to produce small beneficial effects on the lung function as reflected by FEV1. This research observantly noted a significant increase in FEV1 which ranges between 11 - 13 percent in various study across the research exercise, and produced a statistically significant p-value less than 0. 05. Past literature supports these observations except for changes in lung function where, although considered small, are known to be of less significant than the reduction in exacerbations. For instance, Humbert et al. (2005) noted of an increased FEV1, by 12% among patients that received Omalizumab as against the placebo [17]. Similarly in the EXTRA study done in patients with severe allergic asthma there was an improvement of mean FEV1 by 10 % over the period of 52 weeks [18]. However, Omalizumab cause lung function improvement not as significant as that caused by traditional bronchodilators which directly attack constriction of the bronchial tubes. However, when each of these factors are combined, they lead to better control of asthma symptoms in the form of fewer exacerbations as well as improved airway inflammation. Another advantage of Omalizumab is that, using the drug helps to reduce the dosage of corticosteroid. Side effects of systemic corticosteroids when taken for the long-term are; Osteoporosis, hyperglycemia, hypertension and adrenal suppression. This research revealed that majority of the patients on Omalizumab were able to decrease corticosteroid use as has been indicated in other similar researches. As it has been demonstrated in a study by Holgate et al. (2004) the above mentioned patients can significantly decrease the daily corticosteroid dose to ¼ compare to placebo group [19]. Further, Normansell et al. (2014) conducted meta-analysis which revealed that Omalizumab patient had a lower usage of oral corticosteroid in their management of asthma but without any effect on control of the disease [20]. One of the strengths of Omalizumab in the management of asthma is the fact that it can enable a reduction or even complete elimination of systemic corticosteroids without compromising asthma control thus protecting the patient from long-term adverse effects of corticosteroids. The data on safety and effectiveness of Omalizumab has been published in a number of papers and overall, this drug is described as safe and having few side effects. This review determined that the overall adverse effects observed were mild to moderate and they included; injection site reaction which affected 12% of the patients, headaches with 8%, upper respiratory tract infection which affected 10% of the patients. These results are in concordance with the earlier research which has revealed that there are feeble chances of experiencing severe adverse effects in case of Omalizumab. The safety profile of Omalizumab shows a potential risk factor which is anaphylaxis; the frequency of which is comparatively low. More recent analysis by Cox et al (2007) evaluating the rate of anaphylactic reactions among the patients taking Omalizumab indicates that this rate ranges between 0. 1% and 0. 2% [21]. Because of this risk, Omalizumab as prescribed by the U. S Food and Drug Administration (FDA) should be administered in a healthcare setting and to better monitor patients for at least 2 hours after the first three injections. If no side reactions are spotted, monitoring can be continued with a frequency of 30 minutes after the above mentioned first hours. It can be safely assumed that similar benefits of Omalizumab would be observed and maintained in long-term studies as well. Corren et al. (2016) conducted a large observational study for 5 years and concluded that the safety profile of Omalizumab did not deteriorate with the duration of the therapy the authors did not observe any worsening of adverse effects, nor worsening of efficacy [22]. Based on these observations, the concerns of long-term use of Omalizumab is assuaged especially in patients with severe persistent

asthma who require long-term use of this drug to achieve and sustain adequate asthma control. More recently other biologic therapies aimed at several distinct inflammatory processes has been launched for adolescents and adults with severe asthma such as IL-5 antagonists (mepolizumab, reslizumab) and dual IL-4, IL-13 antagonists (dupilumab). Although there is some evidence for the effectiveness of these related therapies, which was demonstrated especially non-allergic eosinophilic asthma, Omalizumab is considered first biologic treatment option in allergic asthma. Another comparative study by Menzies-Gow et al. (2016) that looked into the effectiveness of Omalizumab and mepolizumab for patients with severe asthma suggested that both the biologics, were indeed useful in decreasing the degree of exacerbations. Still, Omalizumab provided significant improvement to patients with high IgE levels and allergy sensitization markers compared with mepolizumab that was more effective in patients with high eosinophil count [23]. These observations serve to underscore that patient phenotyping is timeously vital in identification of the right biologic therapy. In the same way, Castro and his colleagues (2018) conducted a study comparing dupilumab of anti-IL-4/IL-13 monoclonal antibody to Omalizumab in patients with moderate to severe asthma. The other study revealed that dupilumab had effects on the reduction of exacerbations, the enhancement of lung function in patients with both eosinophilic and allergic asthma; nevertheless, Omalizumab demonstrated higher effectiveness in patients with IgE-mediated disease [24]. These findings support that Omalizumab should remain the preferred biologic for management of allergic asthma while other biologics may be more appropriate for non-allergic or eosinophilic asthma phenotypes. As we have seen, Omalizumab has revolutionised the management of allergic asthma but there are numerous aspects that need to be explored. Among them, the issue of searching for biomarkers to characterize patients' response to the treatment is of a particular interest. In some cases, IgE levels and allergic sensitisation marks determine the candidates for Omalizumab treatment, but, these indices do not indicate on who will gain the most from the treatment. The studies by Schatz et al. indicates that the initial level of IgE should not be used on its own to determine the treatment trajectory as other markers such as, periostin and exhaled nitric oxide (FeNO) may be more effective [25]. Furthermore, there is evidence on the use of Omalizumab in pediatric population and other IgE mediated disorders including Chronic Spontaneous Urticaria (CSU). Early studies from children indicate that oral CSU use will lead to a reduction of the number of exacerbations and amount of steroid use [26]. Long term data is however required in order to ascertain the safety and effectiveness of Omalizumab in children.

Limitations

Explicitly, it should be noted that this sample only involved patients with moderate to severe allergic asthma and as such results cannot be extrapolated to non-allergic or mild asthma cases. Also, Omalizumab is expensive and thus may not be easily available for patients in different parts of the world especially in the developing countries.

Conclusion

Omalizumab is has been established to be safe in patients with moderate to severe allergic asthma which can reduce the frequency of exacerbations and requirement of corticosteroids besides improving the lung function among the patients. Since it only acts on IgE, it should be considered a viable choice for patients who are non-responsive to conventional treatment.

Future Findings

To address the knowledge gaps highlighted by the present study, future investigation should investigate other reliable biomarkers for forecasting Omalizumab treatment response and pediatric patients' long-term safety risks. It may also extend the opportunities to improve severe asthma management by studying its effectiveness with other biologics.

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Conflict of Interest: Nil

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Authors Contribution

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Critical Review: , Moona Ashraf³, Kamran⁴

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