ANTI IGE THERAPY IN ALLERGIC ASTHMA AND ALLERGIC RHINITIS

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ABSTRACT
The last few decades have seen a rise in the prevalence of allergic diseases, including asthma and allergic rhinitis. The prevalence asthma is estimated to be around 300 million globally and around 35% in Europe and Australasia and 60 million people in the United States are affected by rhinitis. In India prevalence asthma is estimated to be around 2.38% and 20% to 26% people suffer from allergic rhinitis. Despite varied therapeutic options currently available, many asthmatic patients with moderate-to-severe persistent asthma continue to experience symptoms, causing substantial morbidity and mortality. Immunoglobulin-E (IgE) plays an important role in the pathogenesis of allergic diseases. Omalizumab is a humanized monoclonal anti-IgE antibody, approved for the treatment of severe allergic asthma. Omalizumab inhibits allergic responses by binding to serum IgE, thus preventing interaction with cellular IgE receptors. Various clinical trials have demonstrated that add-on therapy with omalizumab proved effective in reducing asthma-related symptoms, use of systemic corticosteroids and rescue bronchodilators and improving quality of life in severe-persistent allergic asthma patients, who were poorly controlled by available asthma therapies. Drug is relatively well tolerated and has a favorable safety profile. In conclusion, clinical efficacy and tolerability data indicate that omalizumab is a valuable option in the treatment of allergic asthma, in patients who remain symptomatic despite high dose standard therapies.

INTRODUCTION
The last few decades have seen a rise in the prevalence of allergic diseases, including asthma and allergic rhinitis; both are common chronic diseases that affect the quality of life of patients and have a significant economic impact. It is estimated that 300 million people worldwide suffer from asthma and this figure is projected to rise to 400 million by year 2025.1 Asthma accounts for approximately 500,000 hospitalizations each year2, with around 250,000 deaths annually attributed to the disease.1 Allergic rhinitis, previously regarded as a trivial disease affects between 10% and 30% of all adults and as many as 40% of children.3 The prevalence of rhinitis is around 35% in Europe and Australasia4 and it affects approximately 60 million people in the United States, and its prevalence is increasing.5 Allergic rhinitis has a considerable effect on quality of life and can have significant consequences if left untreated causing fatigue, headache, cognitive impairment and other associated symptoms.3

In India, asthma imposes a substantial burden; though there is a paucity of appropriate epidemiological data to determine prevalence for asthma or the allergic asthma. However, a multicenter study by the Asthma Epidemiology Study Group of the Indian Council of Medical Research found the prevalence of bronchial asthma in Indian adults to be 2.38%.6 In India 20 to 26% people suffer from allergic rhinitis and symptoms of rhinitis were present in 75% of children and 80% of asthmatic adults.7,8 With present Indian population estimated to 1 billion plus, number suggest enormity of the burden of rhinitis and asthma in the country. But despite imposing substantial burden both diseases still remains under-recognized, under-estimated and under-treated, in India.

Presently anti-inflammatory and bronchodilation treatments, concurrent with other drugs such as anti-leucotrienes, are effective for most of asthma patients, but these therapies fail to provide
symptomatic relief to all the patients. Hence despite varied therapeutic options currently available, many asthmatic patients with moderate-to-severe persistent asthma continue to experience symptoms even after therapy with inhaled or systemic corticosteroids; accounting for 217,000 emergency room visits and 10.5 million physician office visits every year.8 Although difficult-to-treat patients represent less than 20% of the asthma patient population, they consume a disproportionate share of asthma care resources.9 As these patients require frequent/unplanned medical attention and seek care in emergency departments and other urgent care facilities. The Global Asthma Physician and Patient Survey not only defined an unmet need in asthma treatment, but also revealed that there was a direct relationship between the quality of physician–patient communication, the level of treatment side effects and the extent of patient compliance, highlighting a clear need for improved patient-focused care in asthma.10

Patients with severe persistent asthma who are inadequately controlled despite Global Initiative for Asthma (GINA) step IV therapy, are a challenging population with significant unmet medical need.11 Several reasons have been quoted for this non-maintenance of therapeutic effects, such as patient non-adherence, poor inhalation,12-17 lack of response to pharmacotherapy, presence of co-morbid diseases,18 triggers such as respiratory infections (particularly viral),19,20 indoor allergens21 and environmental exposures.22 This subset of patients who experience frequent exacerbations requiring emergency department visits or hospitalizations, may benefit from novel therapies like anti-immunoglobulin-E (IgE) antibodies, cytokine modulators and DNA vaccinations; designed to target specific mechanisms underlying airway inflammation.9

ROLE OF IgE

It is well recognized that human immunoglobulin E (IgE) plays an important role in the inflammatory response to allergen exposure in atopic patients and plays a critical role in the pathogenesis of atopic-allergic diseases such as those of respiratory tract: rhinitis and bronchial asthma and maintenance of asthma-related symptoms.23-31 Levels of IgE are highly correlated with the development of asthma and bronchial hyper-reactiveness. Elevated serum levels of allergen-specific IgE directed toward environmental or aeroallergens characterize allergic diseases, such as rhinitis and asthma, whereas those against foods are associated with food allergy and eosinophilic disorders of the gastrointestinal tract.32

The principal role played by IgE is in type I hypersensitivity reactions, binding to high-affinity IgE receptors (FcepsilonRI) on mast cells and basophils. Binding to the receptor occurs via the Cepsilon3 domain on the Fc fragment. Levels of FcepsilonRI expression correlate with serum levels of IgE;33 a number of studies have shown a close association between serum levels of IgE so that any reduction can result in significant decreases in expression of this key receptor.34 High-affinity FcepsilonRI are also expressed on dendritic cells (DCs), especially type II DCs that promote Th2 responses. IgE occupancy of the FcepsilonRI on DCs is associated with enhanced allergen uptake and the ensuing allergic responses. IgE also binds to low-affinity receptors (FcepsilonRII, CD23) also expressed on DC and other antigen-presenting cells. Occupancy of this receptor results in amplification of the immune response.35-36

The central role played by IgE in the pathogenesis of allergic diseases including asthma, have made IgE-mediated immunologic pathways an attractive target for therapeutic agents in asthma. The anti-IgE antibody inhibits IgE functions blocking free serum IgE and inhibiting their binding to cellular receptors. By reducing serum IgE levels and IgE receptor expression on inflammatory cells in the context of allergic cascade57 and represent a very interesting option for treatment of asthmatic patients. According to various studies IgE-mediated positive reactions to skin prick tests for common aeroallergens are detectable in a percentage of severe asthmatics, ranging from about 50%-80%.38-39 For all these reasons, anti-IgE therapy was included in 2006 within step 5 of the Global Initiative for Asthma guidelines as add-on treatment to inhaled and eventually oral corticosteroids, long-acting β2-agonists (LABA), and other controller medications, such as leukotriene-modifiers and theophylline.15,40

OMALIZUMAB

Omalizumab is a recombinant anti-IgE monoclonal antibody developed for the treatment of allergic diseases associated with high circulating IgE levels. Omalizumab is currently the only IgE-targeted therapy approved by EMEA (European Agency for the Evaluation of Medicinal Products) and FDA (Food and Drug Administration) for asthma treatment. It is efficacious in the treatment of moderate-to-severe and severe persistent allergic asthma poorly controlled with regular treatment.37,40-41

By reducing serum IgE levels, as well as FceRI and FceRII receptor expression on inflammatory cells, omalizumab inhibits development of inflammatory cascade. His anti-IgE is directed against the binding site of IgE (Cepsiilon3 domain) for the high-affinity receptor, and, as a result, prevents free- serum IgE from attaching to mast cells and other IgE receptorexpressing cells, preventing IgE-mediated responses. Following allergen cross-linking of mast cell-bound IgE, these cells are activated and virtually immediately release a granule-associated substance, such as histamine. Within minutes, de novo synthesis of important lipid mediators (cysteinyl leukotrienes) is initiated from membrane phospholipids. Following a few hours, the activated mast cells are also capable of the transcription, translation, synthesis, and release
of a large number of cytokines, including interleukin (IL)-4, IL-6, IL-9, IL-13, and tumor necrosis factor (TNF)-alpha. This sequential and programmed cascade of events has been implicated in the development of both early and late-phase allergic responses.32,37,40-41

CLINICAL EXPERIENCE

Omalizumab binds circulating free IgE regardless of antigen specificity, indicating that reducing free IgE may inhibit more chronic aspects of allergic inflammation involving T-cell antigen presentation and activation. Drug therefore is potentially useful for atopic disorders caused by either perennial or seasonal allergens, as well as by multiple sensitizations.32,42

Initial evidence of the anti-asthmatic efficacy of omalizumab was demonstrated by investigators in late 1990s. When intravenous administration of the agent (initially called anti-IgE antibody E25) inhibited allergen-induced early and late-phase asthmatic responses.43-45 In key trials confirming its efficacy, omalizumab has been administered subcutaneously. Subcutaneous omalizumab administered to patients with moderate-to-severe asthma at intervals of 2 or 4 weeks reduces the incidence and frequency of asthma exacerbations and also has a steroid-sparing effect as indicated by reduced use of inhaled corticosteroid (ICS).46-48 It also significantly reduces free serum IgE, immediately after the first injection49-50 and alleviates both early- and late-phase asthmatic reactions to inhaled allergens after a standard course of therapy.51-52 Additionally, these studies have also established a relation between reduction in circulating and sputum eosinophilia and nonspecific bronchial hyperresponsiveness.

Since then number of clinical trials have been conducted to examine the efficacy and safety of omalizumab both in adolescents and adults with moderate-to-severe asthma.40 Omalizumab has been given in addition to stable treatment with ICS and other anti-asthma drugs. In patients with moderate-severe allergic asthma, omalizumab reduced asthma exacerbations and corticosteroid requirements when compared with placebo; amid fewer hospitalizations and unscheduled emergency room visits.37,53-54 Overall patients with highest ICS doses and poorest lung function, benefited most from omalizumab therapy.

The pivotal INNOVATE (Investigation of Omalizumab in severe Asthma Treatment) trial,55 demonstrated significant advantage of omalizumab in patients receiving high-dose ICS combined with LABA and additional controller medications. With omalizumab, the rate of clinically significant asthma exacerbations was significantly reduced as compared to the control group (0.68 versus 0.91, p=0.042). There were also improvements in FEV1 percent predicted values (p=0.043), and total asthma symptom scores (p=0.039). Rate of severe exacerbations [defined as a peak expiratory flow or FEV1 < 60% of personal best] was halved (0.24 versus 0.48, p=0.002), and the rate of emergency room visits was reduced (0.24 versus 0.43, p=0.038). The incidence of adverse events was similar in the groups. These findings were further confirmed in a study by Bousquet et al.56

A double-blind, randomized, placebo-controlled trial evaluated patients with severe IgE-mediated asthma who required fluticasone 1000 µg/day or more to control symptoms. Almost half of the patients were concomitantly taking LABA.57 Patients were treated with either omalizumab or placebo. The dose of fluticasone was maintained for 16 weeks and then reduced for 16 weeks. Doses of fluticasone were reduced more in patients who received omalizumab compared to those who received placebo (reductions of 57.2% versus 43.3%, p=0.003). In more omalizumab-treated patients the doses of fluticasone were reduced by at least 50% compared to placebo-treated patients (74% versus 51%, p=0.001). Patients who were on LABA taking omalizumab maintained or improved asthma control and needed fewer rescue drugs despite the substantial reductions in their dose of fluticasone.58

In a meta-analysis of eight trials covering 2037 mild-to-severe allergic asthmatics, omalizumab therapy helped more patients to either reduce or withdraw their ICS use by over 50% [OR 2.50, 95%C12.02 to 3.10] (four trials); or completely withdraw their daily steroid intake: [OR 2.50, 95%C12.00 to 3.13] (four trials) and was also effective in reducing asthma exacerbations as an adjunctive therapy to ICS (OR 0.49, 95%C1 0.38 to 0.64, four trials), or as a steroid tapering agent (OR 0.47, 95% CI 0.37 to 0.60, four trials).59 A recent meta-analysis of eight placebo controlled studies in at least 3000 adults, adolescents and children with moderate-to-severe asthma, published between 2001 and 2009; further confirmed the efficacy of omalizumab.59 This systematic review considered reductions of steroid use and of asthma exacerbations as the primary outcomes; secondary outcome measures included lung function, use of rescue medication, asthma symptoms, and health-related quality of life.

Two recent placebo controlled trials have confirmed the efficacy of omalizumab. Study by Hanania et al, in 850 patients aged 12–75 years showed that, when compared with placebo, 48 weeks of treatment with omalizumab significantly decreased asthma symptoms and exacerbations, as well as the mean daily number of albuterol puffs.60 Other study by Busse et al, in 419 inner city children, adolescents, and young adults with persistent allergic, moderate-to-severe asthma, showed that addition of omalizumab to guideline-based therapy for 60 weeks further improved asthma control, nearly eliminated seasonal peaks in exacerbations, and also reduced the need for inhaled corticosteroids.61

Furthermore the efficacy of omalizumab has been further confirmed in real clinical setting, by several Phase IV studies.
in patients affected by severe persistent allergic asthma treated with omalizumab for 5–12 months.\textsuperscript{62-66}

The SOLAR (Study of Omalizumab in co-morbid Asthma and Rhinitis) study designed to evaluate efficacy of omalizumab in concomitant allergic asthma and rhinitis, in adolescents and adults with moderate-to-severe asthma and moderate-to-severe persistent rhinitis. Omalizumab elicited significant improvements in quality of life related to both asthma and rhinitis, assessed by the Asthma Quality-of-Life Questionnaire and Rhinitis Quality-of-Life Questionnaire. The results from the study were interesting, as asthma and rhinitis two allergic diseases are linked by reciprocal pathogenic connections.\textsuperscript{67}

The other large phase 3 trials of omalizumab in allergic rhinitis have also demonstrated the efficacy of drug in reducing symptoms and improving inherent quality of life for patients with intermittent (seasonal) and persistent (perennial) disease.\textsuperscript{68-70} In patients with rhinitis, initial responses (e.g., ragweed-induced nasal volume) were seen on day 7 and peaked on day.\textsuperscript{42,71}

SAFETY

Omalizumab has been reported to be generally well tolerated with similar incidence of adverse events as compared to that with placebo.\textsuperscript{72} An updated and detailed analysis of the safety of omalizumab included 12 controlled, phase IIb–III clinical trials and more than 5243 patients\textsuperscript{72} Common adverse events in clinical trials included injection site reaction, viral infection, upper respiratory tract infection, sinusitis, headache, and pharyngitis.\textsuperscript{73} These events are not surprising as patients already had immune-mediated asthma, and other immune conditions.

Most of the adverse reactions were similar between omalizumab and placebo use and were mild to moderate in severity.\textsuperscript{74} The most commonly reported adverse events with omalizumab therapy were injection site reactions (45%), viral infections (23%), upper respiratory tract infections (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). Injection site reactions of any severity occurred in 45% of omalizumab recipients and 43% of placebo recipients. Most of these reactions occurred within 1 hour of injection, resolved within 8 days, and generally decreased in frequency with subsequent dosing. This side effect profile has been confirmed by real-life studies which have made it possible to monitor omalizumab-treated patients for up to 3 years.\textsuperscript{40}

Rare events of allergic reactions such as urticaria, dermatitis, and pruritus may occur with omalizumab.\textsuperscript{74} However, the frequency of anaphylactic reactions attributed to omalizumab is low and is estimated to be \textasciitilde0.1% and \textasciitilde0.2% as reported from clinical trials and post marketing studies, respectively. Most of these reactions occur within 2 hours after the first and subsequent subcutaneous injections but some may also appear beyond 2 hours after the injection. Interestingly, no cases of anti-omalizumab monoclonal antibodies have been detected till date.\textsuperscript{75-79} There were no complications associated with the reduced levels of circulating IgE or antibodies against omalizumab observed.\textsuperscript{72}

COST EFFECTIVENESS

The socioeconomic and health care burden imposed by asthma is substantial and is considerably skewed towards patients with severe asthma, particularly when inadequately controlled. As discussed above omalizumab has proven to be effective as add-on therapy in patients with poorly controlled, moderate-to-severe allergic asthma and allergic rhinitis, considerably reducing asthma exacerbations and corticosteroid requirements. However, omalizumab is more expensive than other current asthma medications and the high cost of omalizumab treatment might prove exorbitant for some patients, hence limiting its utility in real day to day clinical practice.

While findings of some of the economic analyses of omalizumab are unfavorable,\textsuperscript{80-82} nevertheless there are published cost-effectiveness analyses which indicate that omalizumab is cost-effective in patients with uncontrolled severe allergic (IgE-mediated) asthma despite other controller medications with a history of severe exacerbations and hospitalization.\textsuperscript{80,83}

Omalizumab as an add-on to optimized therapy significantly improved clinical outcomes in difficult-to-treat patients with severe persistent allergic asthma. Therapy with omalizumab reduced, emergency visit to clinic, number of bed days/hospitalisation and significantly reduced asthma exacerbations and corticosteroid requirement. Although there was incremental effect on cost of treatment with omalizumab use, but cost could be justified by health benefits and overall improvement in quality of life achieved.\textsuperscript{80,85-86}

PATIENT’S SELECTION FOR OMALIZUMAB THERAPY

Omalizumab has been indicated as add-on therapy in patients aged 6 years with severe persistent allergic asthma and following characteristics:\textsuperscript{87,88}

- Multiple documented severe asthma exacerbations
- Symptomatic despite high dose ICS and LABA therapy
- Frequent daytime symptoms or night-time awakenings
- Reduced lung function (FEV1 < 80%)
- A positive skin test or in vitro reactivity (radio allergosorbent test [RAST]) to a perennial aeroallergen
- Body weight between 20-150 Kg. and total IgE 30-1500 IU/ml

The EU prescribing label suggests that the omalizumab
treatment should only be considered for patients with convincing IgE-mediated asthma. Prescribing physicians should therefore ensure that patients with IgE below 76 IU/mL have an unequivocal RAST to a perennial allergen before starting therapy.87

EVALUATING PATIENT’S RESPONSE TO OMALIZUMAB THERAPY

The response to omalizumab treatment varies from patient to patient. Presently, an overall physician’s evaluation of the effects of omalizumab is recommended after 16 weeks of therapy.89 Study has shown that evaluation of omalizumab effectiveness detected at week 16, based physician’s global evaluation of treatment; persisted at week 32 also.90 Results from studies discussed in this article have shown that omalizumab treatment resulted in fewer asthma exacerbations, improvements in asthma symptoms and quality of life, and decreased requirements for both ICS and rescue bronchodilators.37,47-48,53-55,57,79

Collaborating results from different studies, reviews and meta-analysis it can be said, that physician’s overall assessment at week 16, has been found to be the most meaningful measure for identifying responders. The assessment can be based on algorithm of composite measure that may include:87-92

- Improvements in asthma symptoms and quality of life (based on mini-Asthma Quality of Life questionnaire),
- Reduction in clinically significant asthma exacerbations
- Unscheduled hospital/emergency room visits
- Improvement in lung function as determined by Spirometry
- Physician global evaluation of treatment response.

This can be a helping tool for physicians for categorizing responders and determining whether to continue treatment with omalizumab.

PLACE IN THERAPY (CONCLUSION)

The development of a humanized, selective anti-IgE monoclonal antibody is a major clinical advance in interrupting the allergic cascade. Omalizumab, a recombinant humanized monoclonal antibody, is a first anti-IgE antibody approved in more than 27 countries.

From the data of studies summarized in this article, it can emphasized that omalizumab may fulfill currently unmet need in the management of patients with severe-persistent, allergic (IgE mediated) asthma; who remain symptomatic despite treatment with high dose ICS and LABA. This has been is demonstrated by improvements in important clinical parameters as exacerbation rates, emergency visit rates, symptom scores, and quality of life scores. Anti-IgE therapy (omalizumab) is now included in GINA guidelines (Step 5), as add-on therapy with ICS and LABA plus other controller medications.13

Availability of omalizumab in medical practice gives physicians an effective therapeutic option in management of difficult to treat population. The efficacy of omalizumab in reducing allergic airway inflammation and its clinical manifestations, have been demonstrated in several trials, including real-life investigations. The most noticeable effect of drug efficacy is in severe, difficult-to-treat asthmatics. Furthermore, omalizumab has shown to have overall good safety profile and is generally well tolerated. Only rare event of anaphylaxis have been reported and no events of development of serum-sickness, serum-sickness like syndrome or thrombocytopenia are seen.

The cost of omalizumab treatment still remains an issue, but appropriate and thoughtful patient selection based on patient selection algorithm described earlier in this article, can ensure that drug is used in most cost-effective manner to act as useful therapeutic option in asthma care. Although, it is difficult to predict which patients will respond best to omalizumab therapy on the basis of pre-treatment characteristics,87 it is recommended that treatment response is evaluated by the physician after 16 weeks of therapy. Treatment should only be continued in responders.53,87,89-92 This may be a feasible means of selecting patients who should continue treatment.

Overall, omalizumab offers a significant advancement in treatment of difficult-to-treat population and may fulfill an important need in patients with moderate-to-severe allergic asthma.

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