



## OMALIZUMAB: CURRENT STATUS IN ASTHMA THERAPY

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### ABSTRACT

Bronchial asthma is characterised by inflammation in airways leading to hyper-reactivity and spasm of the bronchial smooth muscle, oedema and disruption of the mucosa, and obstruction of the lumen by mucus. The drugs used for asthma are broadly classified into bronchodilators (reliever therapies) and anti-inflammatory drugs (preventer therapies). The preventer therapies mainly include corticosteroids besides mast cell stabilizers, antileukotriene drugs and omalizumab. Omalizumab is a humanised monoclonal antibody which binds to circulating IgE. This compound has demonstrated efficacy in the patient population in a number of clinical studies and its use for severe allergic asthma has been endorsed by several international consensus bodies. It is generally indicated for patients unresponsive to high-dose inhaled steroids and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every two to four weeks depending on dose which in turn depends on the body weight and the IgE level. This review will further discuss the status of Omalizumab in the management of asthma and where does it fit into the treatment of asthma of different severities.

**KEYWORDS:** Omalizumab, bronchial asthma, monoclonal antibody, IgE, corticosteroids, anti-IgE



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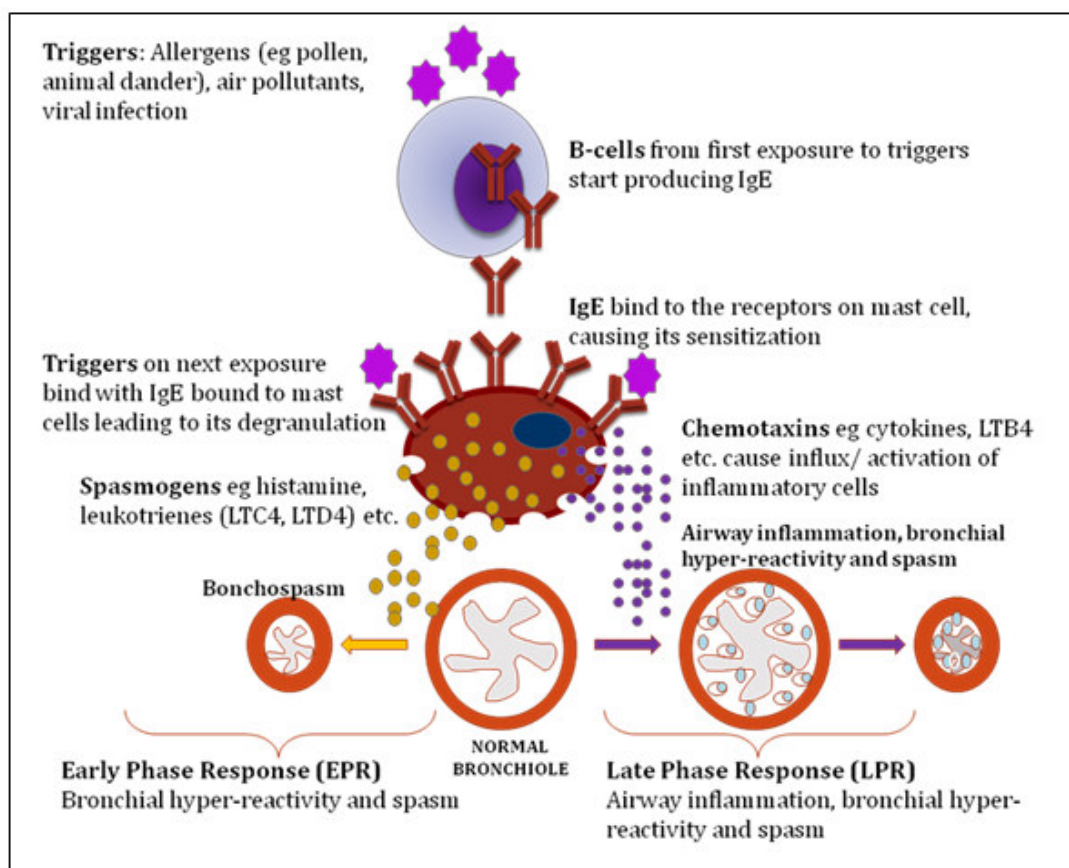
## INTRODUCTION

Bronchial asthma is a chronic inflammatory disease of the airways leading to reversible airflow obstruction and bronchospasm with common symptoms of wheezing, coughing, chest tightness, and shortness of breath. The sharp increase in asthma and other allergic diseases between the early 1960s and late 1980s is perceived to be a consequence of an intense migration from rural to urban regions, from poor developing countries to rich heavily industrialized regions of Europe, Asia and Americas<sup>1</sup>. Our understanding of asthma has increased in past 20 years and safe and effective drugs are available but still it is a serious public health problem. Asthma is thought to be caused by a combination of genetic and environmental factors<sup>2</sup>. Avoidance of triggers is a key component of improving control and preventing attacks. The most common triggers include allergens, smoke (tobacco and other), air pollution, non selective beta-blockers, and sulfite-containing foods<sup>3</sup>. While there is no cure for asthma, symptoms can typically be improved by drug management<sup>4</sup>. The drugs used for asthma are broadly classified into bronchodilators (reliever therapies) and anti-inflammatory drugs (preventer therapies)<sup>5,6</sup>. The preventer therapies mainly include corticosteroids besides mast cell stabilizers, antileukotriene drugs and omalizumab. Omalizumab is a humanised monoclonal antibody which binds to circulating IgE. This compound has demonstrated efficacy in the patient population in a number of clinical studies<sup>7-13</sup> and its use for severe allergic asthma has been endorsed by several

international consensus bodies<sup>13-16</sup>. It is generally indicated for patients unresponsive to high-dose inhaled steroids and have allergy as an important cause of their asthma<sup>5</sup>. Omalizumab is given as a subcutaneous injection every two to four weeks depending on dose which in turn depends on the body weight and the IgE level. This review will further discuss the status of Omalizumab in the management of asthma and where does it fit into the treatment of asthma of different severities.

### **PATHOGENESIS AND THERAPY OF ASTHMA**

Bronchial asthma is characterised by inflammation in airways leading to hyper-reactivity and spasm of the bronchial smooth muscle, oedema and disruption of the mucosa, and obstruction of the lumen by mucus.<sup>17,18</sup> Atopy, or the expression of exaggerated IgE antibody responses against allergens, in early life strongly predicts future airway disease.<sup>19-21</sup> The link between atopy and asthma lies in the development of persistent inflammation in the airways<sup>22</sup>. The inflammation may lead to airway remodelling<sup>23</sup>. The allergic response differs from other immune reactions by its dependence on IgE, its high affinity receptor, FcεRI, and the primary effector cell—the tissue mast cell. The allergic responses following an antigen challenge of a sensitised individual have been designated as early and late phase responses (EPR and LPR) as shown schematically in the figure 1.



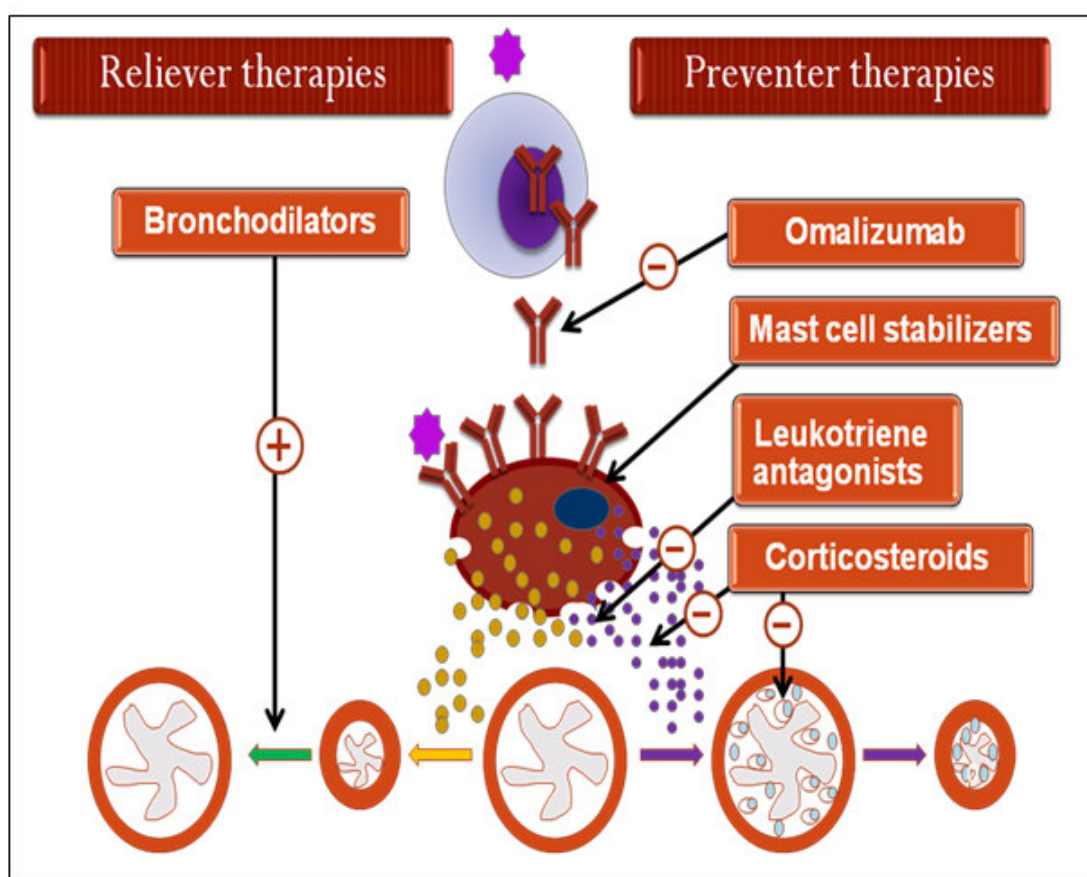
**Figure 1**  
**A schematic representation of the pathogenesis of bronchial asthma**

IgE binds to FcεRI on inflammatory cells in the airways, the gut, and the skin. Cross linking by allergen molecules of a critical mass of IgE antibodies bound to the surface of mast cells initiates EPR<sup>24</sup>. Bronchoconstriction, the clinical manifestation of the EPR in asthma, is confirmed by a fall in forced expiratory volume in 1 second (FEV<sub>1</sub>) within one hour of allergen exposure. Typically, EPR resolves within an hour of onset. LPR, thought to reflect clinical exacerbation of asthma, appears as a second episode of airflow obstruction, 4 to 8 hours after antigen exposure. The bronchoconstriction that develops during LPR is more prolonged, and usually more severe, than that observed during EPR. LPR develops as a result of the action of chemotaxins (cytokines and chemokines) generated by resident inflammatory cells (mast cells, macrophages, and epithelial cells) and recruited inflammatory cells (lymphocytes and eosinophils)<sup>25</sup>. The mast cell is not essential for LPR, however the detection of IL-4, IL-5, IL-6,

IL-13, and tumour necrosis factor-α in this cell, and their release after the cross linking of IgE, support roles for both IgE and the mast cell in LPR and the ensuing persistent allergic inflammation and bronchial hyperresponsiveness<sup>26,27</sup>. IgE antibodies are capable of passive transfer of both EPR and LPR sensitivity to allergen challenge<sup>28</sup>. The identification of IgE receptors on monocytes, eosinophils, dendritic cells, epithelial cells, and platelets along with increased numbers of these receptors in atopic patients suggests a multifunctional role for IgE<sup>29-31</sup>. Thus, cross linking of IgE bound to FcεRI by allergen initiates the release of inflammatory mediators including histamine, leukotrienes, and cytokines and leads to eosinophilic infiltration and inflammation in the affected mucosa or skin. IgE, attached to FcεRII/33 on activated B cells and antigen presenting cells, such as monocytes and Langerhans cells, enhances allergen capture and Th2 cell activation, both

essential processes for initiating and controlling allergic inflammation<sup>32</sup>. Most interestingly, there is documentation that non-atopic intrinsic asthma may be associated with local production of IgE antibodies against unidentified antigens, suggesting that IgE mediated mechanisms may contribute not only to atopic but also to non-atopic disease<sup>33</sup>. The bronchoconstriction, but not the inflammation, oedema, mucosal injury, or excessive mucus secretion, subsides temporarily after the administration of a bronchodilator drug. Various national and international bodies have now expanded the definition of asthma to

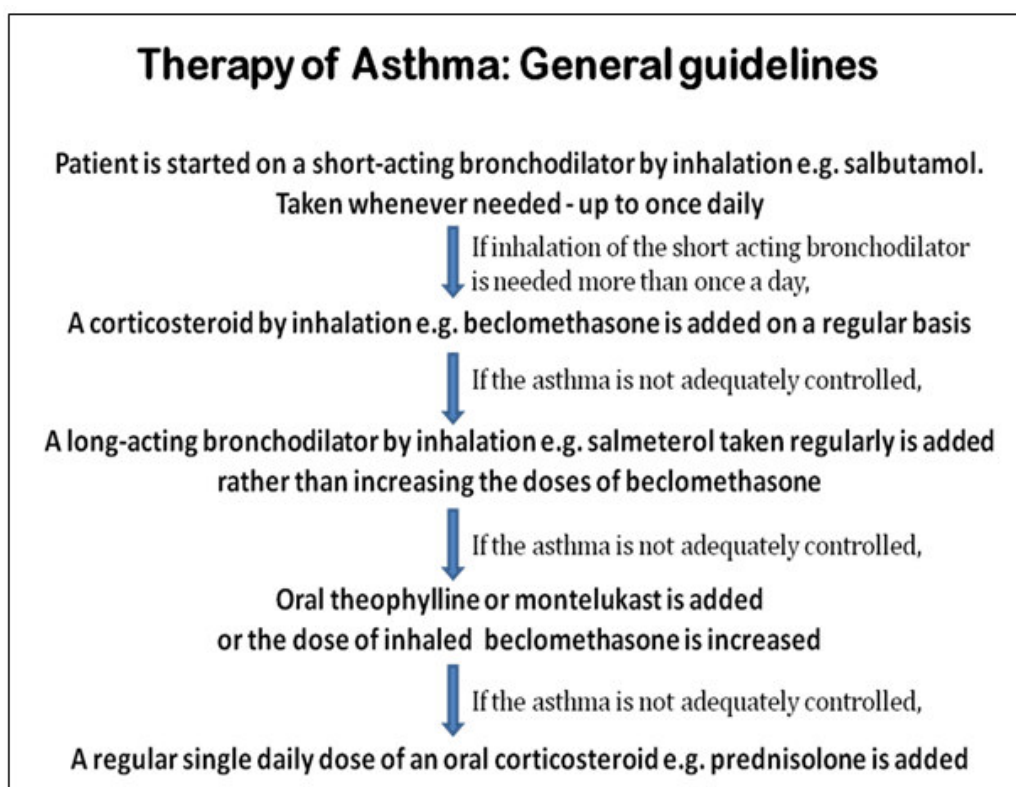
emphasise airway inflammation and airway hyperresponsiveness over the established focus on reversible obstruction and issued guidelines proposing that pharmacological management target these two processes<sup>24</sup>. Therefore, bronchodilators are used to treat the acute attack of asthma while various anti-inflammatory drugs are used to prevent further attacks. The reliever therapy for asthma rests on the use of bronchodilators whereas the preventer therapy includes corticosteroids, mast cell stabilizers, leukotriene antagonists and the anti-IgE antibody, Omalizumab<sup>34-37</sup> (Figure 2).



**Figure 2**  
**Drugs used in bronchial asthma and their target of action**

The most effective preventive therapy for asthma is the administration of inhaled corticosteroids. The ongoing researches in the pathogenesis of asthma indicate the need for new drugs to be explored. Therapy of asthma is generally initiated with the use of a short acting

bronchodilator, to be taken by inhalation as needed. If the individual requires inhalations more than once a day, an inhaled corticosteroid is added on a regular basis<sup>38</sup>. The step care approach for the therapy is outlined in the figure 3.



**Figure 3**  
**General guidelines for the therapy of asthma**

### **OMALIZUMAB IN THE THERAPY OF ASTHMA**

Although a number of bronchodilators coming from different groups provide symptomatic relief the focus is on developing those drugs which prevent or control the inflammation, as it is primarily an inflammatory disease. Obviously preventive drugs would be better than controlling drugs. Success in this preventive aim was achieved when anti-IgE antibodies were found to suppress both early phase allergic response and late phase allergic response.<sup>39</sup> Omalizumab does not bind to IgE that is already bound by the high affinity IgE receptor on the surface of mast cells, basophils, and antigen-presenting dendritic cells.<sup>40</sup> It was approved by FDA in 2003 for moderate to severe allergic asthma.<sup>41</sup> Omalizumab is indicated for patients with moderate to severe persistent allergic asthma, when asthma is inadequately controlled with high-dose inhaled steroids either alone or in combination with a long-acting  $\beta_2$  agonist.<sup>42-43</sup> Omalizumab in clinical trials was found to reduce free serum

IgE, block allergy skin tests in atopic individuals, and significantly suppress early phase allergic response, late phase allergic response and serum eosinophilia in patients with asthma.<sup>44</sup> When given in sufficient doses, omalizumab can reduce free IgE levels by up to 98%.<sup>45</sup> It has shown efficacy in moderate to severe asthma which is not controlled by steroids.<sup>46-49</sup> Omalizumab has not been tested in children below six years of age because of safety concerns like anaphylaxis. However a number of trials have proven its efficacy in children 6-12 years of age. In 2 trials of 926 patients in the age group of 6-12 years, omalizumab was administered after the patients had shown positive skin test or *in-vitro* reactivity to a perennial aeroallergen.<sup>50</sup> All these patients were suffering from moderate to severe persistent asthma. One trial kept efficacy as primary outcome and second kept safety as a primary outcome. In the first trial, statistically significant reduction in the rate of exacerbations was found but other efficacy parameters i.e. nocturnal symptom scores, beta-agonist use,

FEV<sub>1</sub> were not significantly reduced in omalizumab treated group. According to the results of the second trial, omalizumab is not indicated in children <12 of age. It should be remembered, however, that it is not a bronchodilator. Omalizumab has no role in status asthmaticus.<sup>50</sup> In a study involving 334 patients omalizumab was well tolerated. The frequency and types of all adverse events were similar in the omalizumab and placebo group.<sup>51</sup> Number of clinical trials in geriatric population suffering from moderate to severe asthma resistant to steroids have shown that in this age group the efficacy and safety are similar to adult age group<sup>52-53</sup>. However there are some hindrances also in its widespread use. Treatment is costly and being an injectable drug, the compliance is lesser. Omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma. Omalizumab may be used in future for some other clinical conditions also. 50% of patients of chronic spontaneous urticaria cannot be treated with H1-antihistamines; Omalizumab has shown promise in these patients.<sup>54-55</sup>

### **OMALIZUMAB'S DOSE**

Omalizumab is given by subcutaneous route in patients aged > 12 years. The dose and dosing schedule is determined by serum IgE level and body weight<sup>56</sup>. Generally it is given every two or four weeks. The monthly dose of omalizumab is calculated as 0.016 x body weight (in Kg) x IgE level (in IU/mL)<sup>57</sup>. It is available both in the dry powder form and prefilled syringe liquid formulation. For chronic spontaneous urticaria

the dose is 300 mg sc injection every four weeks.

### **OMALIZUMAB'S ADVERSE EFFECTS**

Overall, omalizumab is well-tolerated, and the most frequent adverse events are local skin reactions, usually manifesting as erythema, warmth, swelling, and bruising. Other relatively frequent adverse effects include headache, fatigue, and nausea<sup>58</sup>. Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as the first dose, but has also occurred after one year. Due to risk of anaphylaxis, omalizumab should only be administered to patients in a healthcare setting under direct medical supervision.

### **CONCLUSION**

Omalizumab significantly improves the parameters of asthma like reduction of serum IgE, suppression of early and late phase allergic reactions. This drug offers substantial promise for patients with moderate-to-severe, persistent allergic asthma that is not well controlled. But due to the cost of the drug, limitations on dosage, and available clinical trial data, it is not a first-line therapy. More longer term studies are still required to find out whether it arrests the disease progression or not, it's safety profile, it's effectiveness in non-atopic asthma, it's role in remodeling and role in other allergic diseases.

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