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Review Article

Mepolizumab in Eosinophilic Asthma–Striking a Target that was almost Debunked

Damal Kandadai Sriram[1], Govindaraj Gowri[2], Melvin George[2]

[1]Department of Diabetology and Endocrinology, Hindu Mission Hospital, West Tambaram, Chennai-600045, INDIA.
[2]Department of Clinical Research, Hindu Mission Hospital, West Tambaram, Chennai-600045, INDIA.

ABSTRACT

Bronchial asthma continues to be a disease that has high morbidity and a significant proportion of patients remain symptomatic with frequent exacerbations, particularly the eosinophilic variant asthma. Mepolizumab is an anti-interleukin-5 humanized monoclonal antibody that prevents the eosinophilic inflammation in the lungs. The drug was found to reduce the sputum and blood eosinophilic count which was in consonance with its mechanism of action. However earlier clinical trials with the drug proved to be disappointing, due to the lacklustre performance with end points that focussed on the symptoms of the disease and pulmonary function testing. Subsequently trials focussed on selecting patients who had eosinophilic variant asthma with frequent exacerbations who were resistant to even treatment with systemic corticosteroids. The drug was shown to reduce the frequency of exacerbations in pivotal clinical trials besides reducing the dose of steroid requirement. Mepolizumab is to be given via subcutaneous injection once monthly at a dose of 75 to 250 mg. While the drug does meet an unmet need in the population, the long terms effects, most appropriate dose and frequency of usage and its efficacy in other related hypereosinophilic disorders warrants further exploration.

Key words: Mepolizumab, Bronchial asthma, Eosinophilic asthma, Hypereosinophilic asthma, Exacerbations, Interleukin 5.

Correspondence:
Dr. Melvin George, Consultant, Clinical Research,
Hindu Mission Hospital, West Tambaram,
Chennai-600045, INDIA.
Phone no: +91-9894133697
Email: melvingeorge2003@gmail.com
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INTRODUCTION

Bronchial asthma is a common chronic inflammatory disease of the airways in which the episodic acute limitation of airflow results in symptoms such as wheezing, coughing chest tightness and shortness of breath.[1] In 2011, 235-300 million people were diagnosed globally with asthma and it caused 2,50,000 deaths.[2-4] Asthma is responsible for significant morbidity worldwide. It is the 25th leading cause of disability adjusted life years lost per year. Asthma accounts for 1 of 250 deaths worldwide, however most of these deaths are preventable with appropriate management.[5,6]

The treatment of asthma has largely revolved around the beta adrenergic agonists and corticosteroids given by the inhalational route using a metered dose inhaler. While these drugs do cause relief of symptoms, there are a substantial proportion of patients who continue to exhibit persistent symptoms inspite of being on these medication at maximal doses.[7] Leukotriene antagonists have been a suitable choice only in those with mild persistent asthma and exercise induced asthma. Omalizumab, the first ever monoclonal antibody for asthma, is associated with anaphylactic reactions and neoplasms have occurred in clinical trials.[8] The search for a better drug to target the symptoms and the disease pathophysiology of asthma has taken researchers to explore various therapeutic targets in search of the elusive molecule. One of the fruits of this extensive search has been the discovery of a monoclonal antibody named mepolizumab that was approved by the two major drug regulators, the US FDA and the EMA. We have described in brief the mechanism of action, efficacy, safety, pharmacokinetics, regulatory history of mepolizumab in this review.

Mechanism of action

Mepolizumab is a humanized IgG1 monoclonal antibody. Although the exact mechanism of action of mepolizumab is unknown, the drug is known to bind to interleukin-5 and prevent its interaction with the alpha chain of the interleukin-5 receptor complex. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils, which are involved in the inflammatory cascade of asthma. Patients with eosinophilic variant of asthma have a high proportion of eosinophil content in the sputum, blood and bone marrow. The eosinophils are associated with the airway hyperresponsiveness and inflammation in these patients. Mepolizumab by virtue of its binding potential to the IL-5 is able to neutralize the eosinophilic inflammation in the lungs and thus prevent disease exacerbation.

Efficacy

Clinical Trials

DREAM STUDY: The DREAM study was the largest ever double blind placebo controlled trial that evaluated the effect of mepolizumab in severe eosnophilic asthma. Pavord *et al*[9] Patients were assigned to 4 groups (1:1:1:1) namely mepolizumab in doses of 75 mg (n=154), 250 mg (n=152) and 750 mg (n=156) or placebo (n=159). Compared with placebo group, mepolizumab was found to reduce the number of exacerbations in the study period irrespective of the dose used. There was also a delay in the time to first episode of exacerbation, number of exacerbations requiring emergency visit to hospital. It also showed a reduction in the blood eosinophil and sputum count. The efficacy of mepolizumab was found to be influenced by blood eosinophil count and the number of exacerbations in the preceding year (Table 1).

In a single-center, randomized, double blind, placebo-controlled, parallel-group clinical trial in patients with refractory eosinophilic asthma, patients were assigned to receive 12 infusions of either 750 mg of mepolizumab delivered intravenously (n=29) or matched placebo (150

Table 1: Summary of results of randomized controlled clinical trials with mepolizumab

Authors	Study subjects	Sample size	Decrease in blood eosinophils	Improvement in FEV1	Improvement in symptom score	Reduction of exacerbations	Improvement in QOL	Reduction of steroid dosage
Leckie *et al* (2000)[20]	Mild asthma	24	Achieved	Not achieved	Not measured	Not measured	Not measured	Not measured
Page *et al* (2007)[21]	Asthma uncontrolled with inhaled corticosteroids	362	Achieved	Not achieved	Not achieved	Not achieved	Not achieved	Not measured
Nair *et al* (2009)[22]	Uncontrolled Eosinophilic asthma	20	Achieved	Achieved	Not measured	Achieved	Not measured	Achieved
Haldar *et al* (2009)[10]	Eosinophilic asthma with exacerbations	61	Achieved	Not achieved	Not achieved	Achieved	Achieved	Not measured
Pavord *et al* (2012)[9]	Eosinophilic asthma with exacerbations	621	Achieved	Not achieved	Not achieved	Achieved	Achieved	Not measured
Ortega *et al* (2014)[23]	Eosinophilic asthma uncontrolled	576	Not achieved (Similar)	Achieved	Not measured	Achieved	Achieved	Not measured
Bel *et al* (2014)[11]	Eosinophilic asthma on systemic steroids	135	Achieved	Not achieved	Not measured	Achieved	Not measured	Achieved

ml of 0.9% saline) at monthly intervals between visits 3 and 14 (n=32).[10] Those patients who received mepolizumab reported half the number of exacerbation over one year, as compared to the placebo group (57 vs 109, P=0.02). The mean number of severe exacerbation per subject was lesser in the mepolizumab group than the placebo group (2.0 vs 3.4; RR-0.57; 95% [CI], 0.32 to 0.92; P=0.02). There was a definite reduction in the number of days of hospitalization among mepolizumab users than the placebo group (12 vs 48 days, P<0.001. Mepolizumab reduced the geometric mean of eosinophil percentage in the sputum when compared to the placebo group (1.5% vs. 4.4%) by a factor of 2.9 (95% CI, 1.4 to 6.1; P=0.005). There were no significant changes from the baseline symptom scores, as measured by visual-analogue scales or Juniper Asthma Control Questionnaire (JACQ), FEV1 after bronchodilator use.

The ability of mepolizumab to reduce the corticosteroid requirement was assessed in a randomized, double-blind trial involving 135 patients with severe eosinophilic asthma.[11] As compared with placebo, there was 2.39 times greater likelihood of the reduction in glucocorticoid dosing among mepolizumab users. The patients who were in the mepolizumab arm showed a 50% median dose reduction. Inspite of the reduction in steroid dosing among mepolizumab users, they had a lower annual rate of exacerbations (1.44 vs. 2.12, P=0.04) and a lower symptom score (P=0.004).

Safety

The most common adverse events are headache (21%), nasopharyngitis (22%), Hypersensitivity (1%), chest pain (3%), facial flushing (7%), erectile or ejaculatory dysfunction (7%), rash (7%), pruritus (7%), fatigue (7%), systemic reactions, local injection site reactions.[9-11]

Pharmacokinetics

Mepolizumab is given via subcutaneous injection at a dosing range of 12.5 to 250 mg once every four weeks. The bioavailability of mepolizumab was estimated to be approximately 80% and the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. The central volume of distribution of mepolizumab in patients with asthma is estimated to be 3.6 L for a 70-kg individual.

Precautions

Mepolizumab should not be administered to patients with a history of hypersensitivity or acute exacerbations, acute bronchospasm or status asthmaticus. Clinical trials have not been conducted to investigate the effect of renal impairment and hepatic impairment.

Current Status of the Mepolizumab

Mepolizumab was approved by EMA and US FDA in 2015 for the treatment of severe eosinophilic asthma.[12] Mepolizumab is under clinical trials for the treatment of atopic dermatitis, hypereosinophilic syndrome, eosinophilic esophagitis, nasal polyposis, eosinophilic granulomatosis with polyangiitis (i.e., Churg Strauss syndrome), and chronic obstructive pulmonary disease.[13-17] The drug should ideally be prescribed in patients with the eosinophilic variant of asthma who are poor responders to even systemic corticosteroids. The drug is expected to cost between 10,000 to 15,000 US dollars per year which only adds to the economic burden, but considering the history of drug pricing with monoclonal antibodies, this is least surprising.[18]

The development of mepolizumab has reiterated the importance of choosing the most apt end points and identifying the niche population when designing pivotal clinical trials. Earlier clinical trials with mepolizumab did show reduction in the sputum eosinophil count but failed miserably on most of the clinical end points. This resulted in speculation if IL-5 was a worthwhile druggable target for asthma. The very essence of the concept of the relationship between eosinophilia and allergic response and airway hyperresponsiveness was in the verge of being debunked. On further scrutiny of the study results, it was found that none of the subjects had any proof of eosinophilia in the lungs. Hence subsequent studies focused on identifying subsets of patients with the eosinophilic variant asthma by sputum eosinophil count and used clinical end points such as reduction in the number of exacerbations with mepolizumab when compared to placebo.

Besides mepolizumab, a number of other monoclonal antibodies are in advanced stage of development for asthma such as reslizumab and benralizumab, both of which act on IL-5 and lebrikizumab, an IL-13 inhibitor.[19] It remains to be seen if these drugs could supersede mepolizumab in terms of its efficacy and bring in any other distinct advantage to these patients with recalcitrant asthma. There is a definite need for more studies to explore the best dosing regimen and the duration of therapy and the long term safety of mepolizumab.

CONCLUSION

A considerable proportion of patients with bronchial asthma remain symptomatic with frequent exacerbations even after being given maximal systemic corticosteroids, particularly in those who have the eosinophilic variant. Mepolizumab, by virtue of its anti-IL-5 properties is able to reduce the frequency of exacerbations as well as improve the quality of life in these patients. The drug has also shown to be reasonably safe in the studies carried on till date. Nevertheless, post marketing studies would certainly tell us more about the nature of this drug and to see how much difference it could possibly do in the real world setting to alleviate the agony of patients with bronchial asthma.

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