

Mepolizumab: a new drug in asthma armamentarium

Satyadeo Choubey*, Kunal Ahuja

Department of Respiratory
Medicine, MGM Medical
College, Indore, MP, India

Received: 30 December 2015
Accepted: 03 February 2016

***Correspondence to:**
Dr. Satyadeo Choubey,
Email: chestsd@gmail.com

Copyright: © the author(s),
publisher and licensee Medip
Academy. This is an open-
access article distributed under
the terms of the Creative
Commons Attribution Non-
Commercial License, which
permits unrestricted non-
commercial use, distribution,
and reproduction in any
medium, provided the original
work is properly cited.

ABSTRACT

Bronchial asthma is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment. The current therapy for asthma includes either inhaled corticosteroids alone or in combinations with inhaled bronchodilators with other controller options being theophyllines, leukotriene antagonists and systemic corticosteroids. In step V of Global Initiative for Asthma (GINA) management guidelines Anti Ig E, Omalizumab is recommended in selected patients when everything fails. But still some unmet need is felt in the form of refractory asthma. Mepolizumab, an IL-5 antagonist has been developed in this regard and has been approved by FDA on Nov 4, 2015 followed by European commission on Dec 02, 2015 in view of good results based on clinical trials conducted by GlaxoSmithKline a multi-centre, open-label long-term safety study of 100 milligram (mg) mepolizumab administered subcutaneously (SC) every 4 weeks for 12 months in addition to standard of care in subjects who have severe, refractory asthma and a history of eosinophilic inflammation. This article covers the review of mepolizumab with its advantages in refractory bronchial asthma.

Keywords: Asthma, Anti IL-5, Mepolizumab

INTRODUCTION

Asthma is one of the most common chronic diseases globally and currently affects approximately 235 million people worldwide.¹ The disease has an inflammatory component where cascade of reactions ultimately cause the bronchoconstriction, airway hyperresponsiveness and mucus hypersecretion. Various cell types involved in this process include CD4 helper T cells (Th2), eosinophils, mast cells and monocytes. Th2 type cells release several interleukins (IL) e.g. IL-4, IL-5 & IL-13. While IL-4 & IL-13 cause increased immunoglobulin E (IgE) production, IL-5 helps in proliferation & differentiation of eosinophils.³⁻⁵ The other major source of IL-5 are mast cells (Figure 1).

Management therapy in asthma must include reliever as well as controller medications. The latter are regarded as the backbone of asthma therapy and include corticosteroids, bronchodilators, mast cell inhibitors, leukotriene antagonists, theophyllines etc.

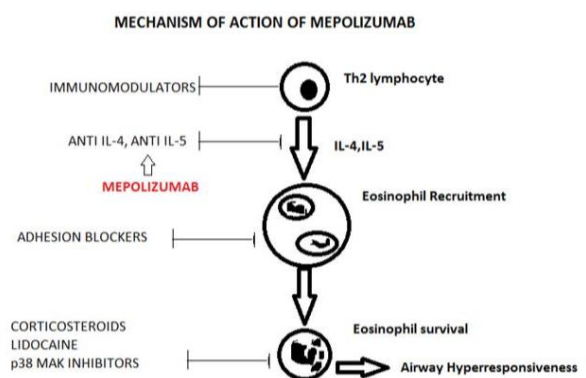


Figure 1: The IL-5 inflammation cascade leading to recruitment of eosinophil in asthma and therapeutic role of mepolizumab.

Corticosteroids are the drug of choice and have to be used in most of the patients for longer term and are limited by their side effects of causing adrenal suppression, lipodystrophy, metabolic syndrome, weight gain and

hypertension though these effects are lesser in inhaled preparations. Global initiative for Asthma (GINA) advocates use of anti IgE antibody Omalizumab in step 5 of its treatment guideline i.e. as a last resort in selected groups.²

Despite all these, there are certain subsets of patients who are not well controlled on the best permutations and combinations of these controller agents labelled usually as having refractory asthma. So there is always a need of discovering some newer molecules to tackle these special phenotypes.

Mepolizumab, an IL-5 antagonist is a new innovation in this regard.

Mepolizumab

Mepolizumab is an IL-5 humanized monoclonal antibody (Ig G1 kappa) approved recently by the United States Food and Drug Administration (US FDA) after it showed good response in the patients with refractory asthma in a trial conducted by GlaxoSmithKline which was an open-label long-term safety study of 100 milligram (mg) mepolizumab administered subcutaneously (SC) every 4 weeks for 12 months in addition to standard of care in subjects who have severe, refractory asthma and a history of eosinophilic inflammation.

Mechanism of action

Mepolizumab binds to IL-5 thus restricting its bioactivity as it is not allowed to bind to the alpha chain of IL-5 receptor complex on eosinophil. Hence further cascade of signalling and over expression of eosinophils is prevented in the blood and tissues (Figure 1).

Clinical trials

It took nine phase 2/3 studies enrolling over 1300 patients for mepolizumab to get approved for clinical use. Three key clinical trials DREAM (MEA112997), MENSA (MEA115588) and SIRIUS (MEA115575) established its efficacy and safety profile. The former one was dose ranging dose selection study while the latter two were pivotal efficacy studies. There was statistically significant reduction in exacerbation in both 97 and 88 studies. There was no significant difference in outcomes using dose of 75 mg or 100 mg. Study 75 showed significant dose reduction of oral corticosteroid in mepolizumab group.

Indications and dosing

Mepolizumab is indicated in patients of asthma aged 12 years and older with eosinophilic phenotype. The recommended dosing is 100 mg once every four weeks to be administered subcutaneously. It is not intended to be used for the relief of acute bronchospasm or status asthmaticus. It is contraindicated in the patients with known hypersensitivity to mepolizumab.

Warnings and precautions

Hypersensitivity reactions e.g. bronchospasm, angioedema, hypotension, urticaria or rash may occur immediately or may have delayed onset. The drug must be discontinued if such event occurs.

Patient may conquer herpes zoster infection during the course of treatment. Varicella vaccination should be advised prior to treatment if medically appropriate.

Corticosteroids should not be stopped abruptly as this may unmask the symptoms previously suppressed or may lead to withdrawal symptoms.

Blocking the eosinophil cascade by mepolizumab may have effect on contracting new helminthic infection. If the new infection does not respond to anti-helminth preparations, mepolizumab may be temporarily discontinued.

Adverse effects

The most commonly reported adverse reactions during treatment were headache, injection site reactions, and back pain and fatigue. Other less common were influenza, urinary tract infections, upper abdominal pain, pruritus, eczema and muscle spasm. Opportunistic infections in the form of herpes zoster may occur.

Drug interactions

No formal drug interaction trial is available so far.

Special populations

Formal data on pregnant patients is not available and requires pregnancy exposure registry though animal data in both pregnant and lactating mother did not reveal any major adverse effects on mother or foetus. The drug is not supposed to be used in paediatric population younger than 12 years of age and based on available data no dose reduction is needed in geriatric population.

Pharmacodynamics and pharmacokinetics

Mepolizumab leads to dose dependent reduction in blood eosinophil count. At 32 weeks the geometric reduction corresponds 84% reduction as compared to placebo. The magnitude of reduction starts as early as 4 weeks of treatment and continues for whole treatment period.

Following subcutaneous injection at recommended dose, bioavailability approximates 80%. Volume of distribution approaches 3.6 litres in a 70 kilogram individual. The mean terminal half-life ($t_{1/2}$) of the drug is 16-22 days. The drug is metabolised by proteolytic enzymes not restricted to hepatic tissue. So there is no issue of hepatic or renal clearance of the drug though limited data is available with creatinine clearance less than 50 ml/minute.

CONCLUSION

Mepolizumab has been approved for difficult to treat eosinophilic asthma and is a very novel drug approach with minimal side effects. It is being investigated for other eosinophilic diseases like hypereosinophilic diseases, eosinophilic oesophigitis, churgh-strauss syndrome. It has been shown to reduce exacerbations and dose of corticosteroids in asthma patients in multiple clinical trials. Along with steroids it helps in attaining a better clinical profile for patient in long term. Although the drug has been approved by US FDA and European commission, but still post marketing pharmacovigilance is required especially for drug interactions, pregnancy and geriatric populations.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. <http://www.who.int/mediacentre/factsheets/fs307/e/> (last accessed 30/12/2015).
2. http://www.ginasthma.org/documents/5/documents_variants/59 (last accessed 30/12/2015).
3. Walsh GM. Advances in the immunobiology of eosinophils and their role in disease. Crit Rev Clin Lab Sci. 1999;36:453-96.
4. O 'Byrne PM. The demise of anti-IL-5 for asthma, or not. Am. J. Respir. Crit Care Med. 2007;176:1059-60.
5. Barnes PJ. Pathophysiology of allergic inflammation. Immunol. Rev. 2011;242:31-50.
6. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf (last accessed 30/12/2015).

Cite this article as: Choubey S, Ahuja K. Mepolizumab: a new drug in asthma armamentarium. Int J Basic Clin Pharmacol 2016;5:543-5.