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## Research Article

# A retrospective analysis of severe asthma treatment with Mepolizumab

## Abstract

Among the different types of bronchial asthma, the allergic one is certainly the most easily found. Allergic asthma is characterized by the presence of IgE antibodies called "reagine", responsible for triggering respiratory allergic crises in the presence of perennial or seasonal specific allergens.

Allergic asthma with severe and persistent symptoms, with high levels of circulating IgE, can be treated with Omalizumab, a humanized monoclonal antibody obtained from recombinant DNA.

It selectively binds to human IgE and reduces the release of histamine and leukotrienes responsible for allergic symptoms.

Unlike traditional anti-IgE drugs, Mepolizumab does not interact with IgE-pathway but interacts with the IL-5 pathway.

Interleukin 5 (IL-5) represents the causal agent triggering growth, activation and survival of eosinophil cells and provides an essential signal for the migration of eosinophils from the bone marrow to the lungs. Some studies suggest that almost 60% of patients with severe asthma present an eosinophilic inflammation of the respiratory tract. Mepolizumab is a monoclonal antibody IgG1 kappa, not glycosylated, that binds to IL-5, preventing its binding to IL-5 receptor on the surface of eosinophils.

The blockade of IL-5 causes a reduction in the production and activation of eosinophils and is an innovative modality for the treatment of eosinophilic asthma.

In this article, we report our experience in the treatment of patients with severe, uncontrolled eosinophilic asthma using Mepolizumab: some of the examined patients had previously been treated with omalizumab with poor symptom control.

## Introduction

Asthma is a chronic airways inflammatory disease characterized by intermittent bronchial obstruction, in most cases reversible spontaneously or by pharmacological treatment.

It is characterized by bronchial hyperreactivity and a progressive decline of respiratory function with bronchial wall remodeling and progressive irreversibility of bronchoconstriction. The functional alterations and symptoms are mediated by numerous pathophysiological mechanisms that include the involvement of various cells of the leukocyte system and the release of numerous mediators. The main cells involved are CD4/T<sub>2</sub>H lymphocytes, mast cells and eosinophils, and the most widely circulating mediators are leukotrienes and interleukin 5 [1,2].

Bronchial asthma affects about 300 million people

worldwide and is responsible for about 250,000 deaths, according to the estimate of the World Health Organization (WHO) and the loss of 15 million DAILY (Life Years Adjusted for Disability); it is widespread all over the world with a different prevalence among the various nations [3,4].

Despite the spread of the GINA guidelines, national and international data show that asthma control is still insufficient; in Europe only 15% of patients treated with inhaled corticosteroid therapy achieve good symptomatic control.

In Italy the situation is better if we take into consideration the asthmatic patients followed by hospital centers where the percentage of patients with a controlled symptomatology reaches 64.4%.

We define severe asthma a subset of patients who need maximal inhalation therapy together with the use of systemic steroids [5].

In recent years, pharmacological research has led to the development of new biological drugs for the treatment of uncontrolled severe asthma: Anti-IgE (Omalizumab) and anti IL-5 (Mepolizumab), which have demonstrated an excellent efficacy and tolerability profile, with an improvement in the rate of exacerbations and quality of life [5–8].

Among the different types of bronchial asthma, the allergic one is certainly the most easily found. Allergic asthma is characterized by the presence of IgE antibodies called “reagine”, responsible for triggering respiratory allergic crises in the presence of perennial or seasonal specific allergens.

Allergic asthma with severe and persistent symptoms with high levels of circulating IgE can be treated with Omalizumab, a humanized monoclonal antibody obtained from recombinant DNA. It is selectively bound to human IgE, inactivating or reducing its ability to bind to the FcεR1 receptor of mast cells and basophils. Thus, it reduces the release of histamine and leukotrienes responsible for allergic symptoms. Unlike traditional anti-IgE drugs, it does not interact with IgE already linked to mast cells and basophils [9].

Interleukin 5 (IL-5) represents the causal agent triggering growth, activation and survival of eosinophil cells and provides an essential signal for the migration of eosinophils from the bone marrow to the lungs. Some studies suggest that almost 60% of patients with severe asthma present an eosinophilic inflammation of the respiratory tract. Mepolizumab is a monoclonal antibody IgG1 kappa, not glycosylated, that binds to IL-5, preventing its binding to IL-5 receptor on the surface of eosinophils. By inhibiting the binding of IL-5 to its receptor, the drug is able to reduce the levels of eosinophils in the blood, at the tissue level and at the level of the sputum [9–11].

Clinical studies (SIRIUS, MENSA) demonstrate an improvement in symptoms and respiratory function in patients with allergic asthma with more than 300/mcl eosinophils. These patients reduce steroid use and the number of exacerbations. Adverse events in these studies were similar to placebo groups [6].

The blockade of IL-5 causes a reduction in the production and activation of eosinophils and is an innovative modality in the treatment of asthma.

In this article, we report our experience in the treatment of patients with severe, uncontrolled eosinophilic asthma using Mepolizumab. We have treated 7 patients with Mepolizumab since June 2017, two of whom had previously been treated with Omalizumab with poor symptom control.

## Methods

We did a retrospective study on patients followed by the division of Lung Disease, Sandro Pertini Hospital, Rome, Italy. We enrolled adult patients (Tables 1,2 for the characteristic of population) with severe eosinophilic asthma who had had at least two exacerbations in the previous year requiring treatment with oral corticosteroids, with regular use of high-dose inhaled corticosteroids in the 12 months before our visit and intense dyspnea.

**Table 1:** Mepolizumab.

Demographics
Sex, No (%) 3 male, 42%, 4 female, 58%
Age 64 years ±10.5
Asthma duration 30.2 years ±7.7
Smokers 28%
Comorbidities: 1 male with bronchiectasis, 1 female with churg-Struss Syndrome, 1 male and 1 female both with sever sinusitis
Eosinophilic Count in the 12 month before the 7%±0.03% (780/mcl±26)
Treatment
Treatments durinh observation ICS 100%, LABA 100%, LRA 42% LAMA 58%
Atopy, total IgE 3pz Omalizumab- >Mepolizumab, the first was male with Eo 490/ mcl and Ige 50 KU/L, the second one was female with Eo 11560/mcl and IgE 700 (KU/L)

The patients also had airflow obstruction as indicated by a pre-broncodilator FEV<sub>1</sub> less than 80% predicted. We enrolled non- or former smoker patients and excluded actual smokers and patients who received Omalizumab within 180 days before the first administration of Mepolizumab.

All patient had an eosinophil profile shown by a blood count, as indicated by the registration studies and they were then subjected to a recruitment visit. All patient were monthly visited at each administration and the dyspnea was evaluated with mMRC questionnaire. The mMRC scale measures the sensation of dyspnea as the person perceives it. The severity of dyspnea is rated on a scale of 0 to 4 [12–13].

The patients received a subcutaneous injection of Mepolizumab 100mg (®GlaxoSmithKline) and we evaluated every month until the twelfth month of treatment not only for the dyspnea but also for the use of rescue medication and the number of exacerbations (as indicated by the GINA guidelines the exacerbation phase of asthma is a deterioration symptomatic and functional acute or sub-acute compared to the patient's normal status). We do not report systemic and local site reactions.

## Results and Discussion

Severe asthma is defined as a disease that can only be controlled with high dose inhaled corticosteroid plus a second maintenance medication and/or systemic corticosteroid.

The Gina guidelines recommend excluding a poor adherence to therapy and the presence of triggering factors such as smoking before diagnosing severe asthma.

Recurrent asthma exacerbations are particularly frequent in the subset of patients with blood and sputum high levels of eosinophil.

Interleukin (IL)-5 is the major cytokine that plays an important role in eosinophilic production, proliferation and chemotaxis.

Novel studies on biological therapies have reported positive results with the use of Mepolizumab. It is an IL-5 antagonist

monoclonal antibody approved by the Food and Drug Administration (FDA) in November 2015 and used successfully in patients whose exacerbation are eosinophilic related.

In our study Mepolizumab has been used to treat severe eosinophilic asthma in seven patients previously treated with high dose of oral corticosteroid for frequent exacerbations with a maximal inhalation therapy (GINA 4-5) and poor symptom control.

Two of the selected patients suffered from nasal polyposis; after an otolaryngologist visit, one of them showed a complete resolution of the nasal polyposis after two administration of Mepolizumab, whereas the other one after 6 month told us only symptoms resolution.

One patient was suffering from Churg-Strauss Syndrome, that is treated as severe asthma (Mepolizumab 100mg/4 weeks), one patient was receiving Mepolizumab after hospitalization in ICU with invasive mechanical ventilation for near fatal asthma.

Although the test of dyspnea with mMRC scale is not a test of the quality of life has shown immediately an improvement

improvement in the quality of their breath and therefore of their daily life. In all patients with severe asthma in fact dyspnea is strongly disabling. The evaluation of subjective dyspnea, before and after drug administration, was performed in all patients.

Four patients reported a pre-treatment value of 2, two equal to 3 and only one equal to 5.

After treatment with Mepolizumab all patients reported a dyspnea value of 0 of mMRC scale already at the first medical examination carried out within one month after the administration of Mepolizumab.

Table 2 shows how patients have shown an immediately improvement in dyspnea accompanied by a significant reduction in exacerbations, as shown by the registration studies of mepolizumab (DREAM and MENSA).

We observe an improvement in thoracic objectivity with a reduction in wheezing and an improvement in pulmonary ventilation in all patients.

Blood eosinophilia also for us, as for Yancey W et al., has proved to be an effective biomarkers both for the indication and also for the follow-up of severe asthma. The reduction of eosinophilia is in fact accompanied by a significant clinical improvement and a reduction in dyspnea [14].

Respiratory measurements at the twelfth month of Mepolizumab treatment, showed slight improvement of FEV<sub>1</sub>, as underlined by the table where the average of the FEV<sub>1</sub> pre-treatment is 1.67±22 lt and after six months of treatment it is 1.69±6 lt (Table 2) [15].

Dyspnea in asthma can be associated with a normal FEV<sub>1</sub> and does not correlate with the FEV<sub>1</sub> value. Furthermore Spirometry in 30% of asthmatic patients may be normal even if the patient complains of dyspnea [16,17].

Table 2: Mepolizumab.

Data	Before mepolizumab	After 12 month of mepolizumab
History of exacerbations		
-number of exacerbations in the previous year (media)	2.2	0
-number of average exacerbations in the previous year with > 1 access in ER/Ward (media)	0.3	0
Eosinophilic counts		
>150mcl	>400/mcl 100%	>150/mcl 40%
150-300mcl		150-300mcl 60%
300-400mcl		
>400mcl		
Eev <sub>1</sub> before	65%±22 (1.67±0.37)	69%±6.1±0.21
bronchodilatation (media DS)		
Perceived dyspnea mMRC	2.5±0.7	0
Dose of oral corticosteroids (prednisone)	10mg	0

Dyspnea is related to the increase in ventilation resistive load which lead to high lung volumes ventilation induced by air flow limitation, with reduction of inspiratory capacity.

According to our observation, the dyspnea in these patients has progressively improved thanks to a decrease of airway secretions, caused by a reduction in the phlogistic state of the whole lung, which led to a reduction of the airflow limitation and an improvement in ventilation. In agreement with the analysis of Ortega HG et al., we also document more an improvement in the number of exacerbations and a significant reduction in systemic steroid intake rather than an improvement in FEV<sub>1</sub> [18,19].

The data will be reviewed as soon as a larger population is available and will be integrated with the study of inspiratory capacity and residual volume.

We did not observe any collateral, local and systemic effect in all the seven patients treated for severe asthma.

Two patients in the previous 6 months were treated with Omalizumab with a partial benefit and were included in the Mepolizumab group because they presented not only a high IgE plasmatic concentration but also a high eosinophilic blood count.

Recent results from a *post-hoc* analysis suggest that patients with severe eosinophilic asthma previously treated with Omalizumab may have a positive response if subsequently treated with Mepolizumab [20].

Basing on this first experience we have realized that the selection of patients (precision medicine) who access to this type of treatment is the basis of the success of biological therapy.

What emerges as surprising in our evaluation is the complete suspension of systemic steroid therapy in all our patients with maintenance of symptom control.

The data, although limited to a small population, show how add-on therapy with Mepolizumab offers a significant health benefit for these patients not only for the control of severe asthma but also for the reduction of possible side effects provoked by long therapies with systemic steroids.

No asthmatic exacerbation was really severe and no patient was hospitalized, while a very high pre-treatment exacerbation rate had been recorded.

## Conclusion

Our initial and limited experience has showed that Mepolizumab represents a therapeutic option for a specific subset of patients with severe asthma. It has been showed to improve symptoms, to reduce asthma exacerbation and to reduce glucocorticoid use.

The drug, as already demonstrated in literature, has shown a good safety and tolerability. Ongoing clinical trials evaluating the use of this therapy for eosinophilic granulomatosis, eosinophilic esophagitis and hyper eosinophilic syndrome are under way.

We think that the keystone in the treatment of asthma is the selection of the phenotype because it allows to implement precision medicine.

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