ORIGINAL RESEARCH

Effectiveness and safety of mepolizumab in severe refractory eosinophilic asthma: results in clinical practice

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Abstract

Background: Asthma is an inflammatory disease of the airways with symptoms that vary over time and intensity, sometimes leading to disability or even death. Eosinophilic asthma accounts for 25% of cases of severe asthma. It is mediated by eosinophils regulated by interleukin-5 (IL-5), the target of mepolizumab, which has been recently licensed as an add-on treatment of severe refractory eosinophilic asthma. The aim of this study was to evaluate the effectiveness and safety of mepolizumab in clinical practice.

Methods: A multicentre, retrospective, and descriptive study covering a year was conducted in a province of Spain with more than 500,000 inhabitants. Every patient prescribed with mepolizumab since its introduction into the hospital was included in the study. Clinical parameters were collected from the pharmacists' counselling reports from electronic prescription software and electronic patient records. Effectiveness was assessed as a decrease in the exacerbation frequency and/or a reduction in the use of oral corticosteroids (OCS) compared to the previous year.

Results: A total of 25 patients were studied, but only 23 could be evaluated by the cut-off date. A decrease in the exacerbation frequency was observed in 19 (82.6%) patients, 11 of them without any exacerbation during the treatment. A relative reduction of 87% in the exacerbation rate per year was obtained. A total of 15 patients were on regular OCS – 9 patients (60%) reduced their average dose, whilst 4 (26.7%) patients completely abandoned OCS. Safety was evaluated based on reported adverse effects. Adverse events were observed in 12 patients, the most common being headache, arthralgia, and dizziness/nausea.

Conclusion: Mepolizumab has been shown to be effective based on the high decrease in the exacerbation frequency and reduced use of OCS. Reported adverse effects were mostly mild and appeared in half of the patients; some of the adverse events had not been previously described in pivotal trials.

Keywords: adverse drug reaction, asthma, biological therapy, eosinophils, interleukin-5, medication therapy management, mepolizumab, treatment outcomes.

Introduction

Asthma is a common, chronic, and heterogeneous inflammatory disease of the airways with diverse phenotypes sharing similar clinical manifestations, but different aetiologies. Its prevalence varies in each country, oscillating between 2 and 11.9% of the population.

Its pathogeny is caused by diverse cells and inflammatory mediators, partly conditioned by genetic factors. It is characterized by bronchial hyper-responsiveness (BHR) and a variable obstruction of the air flux, totally or partially reversible, reacting to drugs or to spontaneous resolution. It is defined by respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and coughing, that vary over time and intensity.[1]

The treatment of asthmatic patients is organized by therapeutic steps depending on the level of control of the symptoms and exacerbations. Many drugs may be necessary to control the disease such as inhaled corticosteroids (ICS), long-acting β_2 agonists (LABA), short-acting β_2 agonists (SABA) or medium-dose ICS/LABA as-needed, leukotriene receptor antagonists (LTRA), oral corticosteroids (OCS), or even tiotropium or theophylline, and add-on treatment on each phenotype. If patients have persistent symptoms

or exacerbations despite optimal therapy, all of the therapeutic repertoire is needed (Steps 5 and 6 of the Spanish Guideline for Asthma Management [GEMA], Step 5 of the Global Initiative for Asthma [GINA]) – the stage is classified as severe asthma.[1,2] This category is associated to higher direct and indirect economic costs,[3] lower quality of life, and health complications associated with the chronic use of OCS.[4]

Despite optimal treatment, the asthma of some patients cannot be well controlled. This is estimated to happen in 3.9% of the asthmatic population and is considered to be severe refractory asthma.[2] At this point, it is important not to confuse severe asthma and uncontrolled asthma. Severe asthma is defined by poor asthma control despite appropriate management of symptoms and risk of negative outcomes, whilst uncontrolled asthma can be related to poor adherence or to incorrect use of the drug. According to the latest estimation of the World Health Organization (WHO), there were 383,000 deaths related to asthma in 2015.[5]

Although severe asthma presents a substantial heterogeneity in clinical and inflammatory features, it is distinguished by persistent asthma symptoms, frequent exacerbations, persistent loss of lung function, and important comorbidities. ICS are the basis of treatment, whilst other therapeutic options are as follows: optimization of ICS/LABA dose, OCS, add-on treatment without phenotyping (e.g. tiotropium), or phenotype-guided add-on treatment (e.g. omalizumab if there are elevated IgE levels; mepolizumab, reslizumab, or benralizumab if there is severe eosinophilic asthma).

Eosinophilic asthma is characterized by the presence of eosinophils in bronchial biopsies and sputum, despite treatment with high doses of glucocorticoids, and it is said to account for more than 25% of the cases of severe asthma. It entails alterations in the metabolism of arachidonic acid and, occasionally, inflammation mediated by T helper-2 lymphocytes (Th2). Interleukin-5 (IL-5) is produced by Th2 cells, group 2 innate lymphoid cells (ILC2), and eosinophils themselves amongst other cells and is the key cytokine responsible for maturation, activation, proliferation, and survival of eosinophils.[6]

Mepolizumab is a humanized monoclonal antibody targeting human IL-5, blocking it from binding to its receptor, therefore inhibiting IL-5 signalling and reducing the production and survival of eosinophils. It is used as an add-on treatment in severe refractory eosinophilic asthma (SREA).[7] Mepolizumab is the first biologic agent authorized for SREA but it is expensive. Because of that, the Ministry of Health, Social Services and Equality has taken a stand, and a Therapeutic Positioning Report has been published by the Spanish Agency of Medicines and Medical Devices.[8] This drug is dispensed at the Hospital, which brings a new profile of patients to the Pharmacy Department. It is noticeably changing the treatment for these patients but there is not enough knowledge about it yet. Available studies about their effectiveness and safety in real-life

conditions are limited. Therefore, it is very important to study it more in depth.

It is important to point out that randomized clinical trials (RCTs) are the "gold standard" for evaluating treatment outcomes. They are designed under optimal conditions and therefore have a high internal validity. However, these ideal settings are sometimes very far removed from real-life conditions. Patients can be carefully selected, excluding a large part of the population which can be underrepresented in these types of studies. This lack of generalizability might be related to a limited external validity.

At this point, real-life studies are a powerful tool to evaluate effectiveness and safety in everyday practice. They have inherent limitations, mainly due to the absence of randomization and the higher risk of bias, but it is necessary to acknowledge their advantages, such as nonselected population, realistic therapy adherence, routine practice setting, and longer duration or utility to detect late side effects. Comparison of results obtained in RCTs and real-life studies can provide complementary information about the benefits and side effects of a recent drug.

This approach to the differences between RCTs and real-life studies, showing their advantages and limitations, has been addressed by some authors.[9] Some articles even emphasize this variety of settings in the treatment of severe asthma, as the one carried out by Caminati and colleagues in which omalizumab efficacy and safety outcomes were compared in RCT and real-life studies.[10]

The recent commercialization of mepolizumab means that very few real-life studies have been carried out and published. For this reason, this study aims to show an approach to daily practice, presenting effectiveness and safety outcomes of mepolizumab in SREA. The importance of the evaluation of its clinical results is based on the fact that many patients with SREA have uncontrolled symptoms, which are related to high economic costs, lower quality of life, and a higher healthcare demand.

It is also essential to monitor its adverse effects, as the only available information comes from the pivotal studies, which are developed in a controlled environment amongst carefully selected patients and are not easily extrapolated to ordinary patients in the daily practice. At this point, adverse events monitoring takes special relevance in the detection and notification of those which did not appear in clinical trials.

Thus, the aim of this study was to analyse the effectiveness, clinical outcomes, and safety of mepolizumab.

Methods

A retrospective descriptive study of the use of mepolizumab covering the three public hospitals of a province of Spain with more than 500,000 inhabitants was performed. The study started when mepolizumab was included in the

Pharmacotherapeutic Guide, and it was conducted for over a year from October 2017 to October 2018.

The study was designed taking into account the STROBE statement and was approved by the Clinical Research Ethics Committee of the province to which the three public hospitals are assigned. Patients' informed consent were not obtained because this was a retrospective study where neither the treatment nor the following of the patients were affected, and the data were always anonymized and confidential. Every single patient prescribed with mepolizumab in any of the three hospitals was included in the study.

There is a Therapeutic Positioning Report published by the Spanish Agency of Medicines and Medical Devices summarizing clinical trial data and recommending usage criteria. This report establishes two situations in which mepolizumab could be more beneficial[8]:

- Patients with SREA and eosinophil count ≥500 cells/µL.
- Patients with SREA and eosinophil count <500 cells/µL and:
  - More than two severe exacerbations in the last year requiring ≥2 cycles of oral or systemic corticosteroids or a rise in maintenance dose for at least 3 days.
  - More than one severe exacerbation in the last year requiring hospitalization, intensive care unit admission, or mechanical ventilation.

In the last situation, the prescription of mepolizumab has to be assessed individually in patients with SREA and uncontrolled symptoms.

Demographic characteristics (gender and age) and the following variables were analysed: previous use of omalizumab, exacerbation frequency, use of OCS, pulmonary function (Forced Expiratory Volume in one second [FEV_1]), blood eosinophilia, improvement of the quality of life (evaluated using the Asthma Control Test[2] (ACT), a questionnaire previously validated with five questions and five answers each), and adverse effects (evaluated using the Karch–Lasagna algorithm).

The variables analysed at the end of the study were compared with the same variables obtained at the beginning of the study.

Exacerbations were defined in the Therapeutic Positioning Report as any severe peak of symptoms that requires intensive care unit admission, mechanical ventilation, hospitalization, a visit to the emergency room, a cycle of OCS, or an increase in the maintenance dose of OCS.

Data were collected from the pharmacists' counselling reports from both the Electronic Prescription Software, Prisma® and Silicon®, and the Program of electronic patient records, Diraya®.

Patients came to the Hospital Pharmacy Department every 4 weeks where they answered the ACT and added questions about exacerbation frequency, use of OCS, adverse effects, and adherence to the treatment.

Patients were also evaluated 4 months after starting the treatment by the pulmonologist to assess improvements in the parameters analysed, measuring the benefit obtained and possible secondary effects. Clinical benefit was defined as a decrease in the exacerbation frequency, the use of OCS, or an improvement in the pulmonary function. Nonresponsive patients were those who did not show a decrease in the exacerbation frequency or the use of OCS, or improvement in the pulmonary function or quality of life.

Adverse drug reactions (ADR) were considered by pharmacists to be related to mepolizumab if some of the following circumstances were present: previous reports of the ADR, coherent temporal relationship, response to dechallenge or stopping the drug, response to rechallenge or re-exposure, alternative causes for the ADR, or confirmation of ADR by objective evidence.

Results

There were 25 patients studied, 22 (88%) of them were female, with a median age of 51 (21–68) years – 10 (40%) had been previously treated with Omalizumab. However, two (8%) patients had been treated with mepolizumab for less than 4 months and parameters have not been evaluated yet.

From the 23 patients evaluated, 20 (86.9%) obtained benefit from mepolizumab and 3 (13%) stopped the treatment. The revocation of the treatment was due to lack of effectiveness in two patients (male) after the first evaluation by the pulmonologist, both patients showed persistent symptoms, visits to the emergency room, and cycles of OCS during the treatment. The treatment was also stopped in one patient due to hypersensitivity reactions (one female) as assessed by interview with the pharmacist.

The median of the number of exacerbations per year in the patients studied was 4.5 (range [1–14]). The exacerbation frequency decreased in 19 (82.6%) patients, most of them (11 [47.8%]) without any exacerbation since they started the treatment with mepolizumab. At the end of the study, the median of exacerbations per year was 0.58 (range [0–5]) (Table 1).

At the start of mepolizumab prescription, 15 patients were on regular OCS – the average dose was 14.8 mg of prednisone or equivalent (range [5–25]). At the end of the study, the use of OCS decreased in nine (60%) patients, out of which four (26.7%) completely abandoned OCS. Only 11 (73.3%) patients were still on regular OCS and the median dose was 10 mg of prednisone or equivalent (range [5–25]) (Table 1).

Pulmonary function was evaluated in nine (39.1%) patients measuring FEV_1. Only three (13%) patients had better outcomes regarding FEV_1, improving by 15, 20, and 32% on the value obtained before the beginning of the study. For the remaining patients, four (17.4%) maintained the same values of FEV_1 and one (4.3%) final patient obtained a worse result, with a decline of 27% specifically.

Table 1. Frequency of clinically relevant exacerbations and use of oral corticosteroids.

	Mepolizumab 100 mg sc.		Previous year
Clinically relevant exacerbations (23 patients)			
Exacerbations per year (median)	0.58		4.5
Relative reduction (%)		87%	
No. of patients with less exacerbations		19 patients (82.6%)	
Use of oral corticosteroids (15 patients)			
Average dose prednisone or equivalent	10 mg		14.8 mg
Relative reduction (%)		32.40%	
No. of patients with less OCS		9 patients (60%)	

SC, subcutaneous

Table 2. Classification of reported adverse drug reactions in MedDRA terminology.

SOC	LLT	No. of patients
Nervous system disorders	Headache	8 (34.7%)
	Dizziness	6 (26%)
	Somnolence	1 (4.3%)
	Anosmia	1 (4.3%)
	Ageusia	1 (4.3%)
General disorders and administration site conditions	Fatigue	2 (8.6%)
	Administration site pruritus	2 (8.6%)
	Asthenia	2 (8.6%)
	Injection site pain	1 (4.3%)
Musculoskeletal and connective tissue disorders	Arthralgia	8 (34.7%)
	Back pain	4 (17.4%)
Gastrointestinal disorders	Nausea	6 (26%)
Skin and subcutaneous tissue disorders	Alopecia	2 (8.6%)
Immune system disorders	Drug hypersensitivity	1 (4.3%)

SOC, System Organ Class; LLT, Lowest Level Term

Blood eosinophilia was normalized in 12 (52.2%) patients, remained elevated in 3 (13%) patients, though lower than the previous year, and it was not analysed in 8 (34.7%) patients. With reference to these three patients with persistent blood eosinophilia, one had reduced both exacerbations and OCS, one had reduced only exacerbations, and one did not reduce neither exacerbations nor OCS.

In addition, the quality of life evaluated with the ACT test improved in 19 (82.6%) patients compared with the results obtained before the treatment started. At the beginning of the study, the mean value of the ACT test was 11.1 (range [5–14]) and by the end of the study the mean value was 18.4 (range [9–25]).

Lastly, 12 (52.2%) patients acknowledged ADR (Table 2). These started at different times of the treatment, mainly after the first administration and all of them in the first 3 months. The most common adverse effects reported by the patients were headache (34.7%) evaluated as possible (five points), arthralgia (34.7%) and dizziness/nausea (26%) both evaluated as probable (four points).

Discussion

Reductions in the exacerbation frequency and the use of OCS, used in our study as a measure of effectiveness, were the primary efficacy endpoints of the pivotal trials DREAM, MENSA, and SIRIUS.[11–13]

In our study, mepolizumab was shown to be effective in most of the patients. The exacerbation frequency decreased in 83% of them, with 47.8% not having any exacerbation during the treatment.

Pavord and colleagues evaluated the efficacy of intravenous mepolizumab in the DREAM study in three different groups: 75, 250, or 750 mg. The reduction in the rate of clinically significant exacerbations was 48% in the 75 mg group, 39% in the 250 mg group, and 52% in the 750 mg group.[11]

In the MENSA trial, Ortega and colleagues observed a relative reduction in the exacerbation rate of 53% in the group receiving mepolizumab 100 mg subcutaneously; whereas, in the mepolizumab 75 mg intravenous group, the relative reduction was 47%.[12]

In our study, the reductions in the exacerbation frequency were better than those reported in the pivotal trials. This could probably be explained because mepolizumab was included in our Pharmacotherapeutic Guide to be used following the recommendations established in the Therapeutic Positioning Report.[8] In the MENSA study, Ortega and colleagues observed that the response to mepolizumab with reference to exacerbation frequency was more favourable in patients with higher eosinophil count, decreasing in 73% of the patients in the subgroup with eosinophil count ≥500 cells/μL.[12]

In our study, of the 15 patients with regular OCS, 9 (60%) patients reduced their dose and 4 (26.7%) of them even abandoned OCS after a progressive and controlled reduction. These were the most important objective parameters in our study. Reduction in the use of OCS was analysed by Bel and colleagues in the SIRIUS trial. They obtained a median percentage reduction of 50% from baseline in the daily OCS dose in the mepolizumab group; whereas, in the placebo group, there was no reduction.[13] Bel and colleagues did not divide the results of reduction in the use of OCS by eosinophil count; however, this relation could be evaluated in further studies.

With regard to the safety of mepolizumab in our study, 52% of the patients showed adverse reactions. Despite this, mepolizumab should still be considered safe to take given that the adverse effects were mild and self-limited, and compromised treatment on only one occasion.

The most frequently reported adverse events in both MENSA and SIRIUS trials were nasopharyngitis and headache. Adverse effects were reported in 83% of the mepolizumab group in the SIRIUS study and 84% in the intravenous mepolizumab group and 78% in the subcutaneous mepolizumab group in the MENSA study. In the MENSA study, the incidence of adverse events considered by the study investigators to be related to mepolizumab was 17% in the intravenous group and 20% in the subcutaneous group.[12,13]

Adverse effects were also frequent in our study, all categorized as possible or probable with the Karch–Lasagna algorithm. This could be related to the complexity of the patients with SREA, which frequently have many comorbidities, and are not as monitored in daily practice as they are in the clinical trials.

The adverse effects reported in our study were not severe; however, only headache was described in the pivotal trials[8] and in the summary of product characteristics.[7] Possible adverse effects should be monitored with post-commercialization studies, as the pivotal trials are designed to evaluate efficacy and are not ideal to evaluate safety.

In our country, some hospitals have also carried out their own studies to evaluate efficacy and safety of mepolizumab in real-life conditions. Patients included were very similar to those in this study, with a median age between 52 and 63 years, and had been previously treated with omalizumab in a range of 38–80%.[14–20] In our study, the average age was 51 years and 40% of the patients studied had been previously treated with omalizumab. In these real-life studies, a reduction in exacerbation frequency (44–100%) and use of OCS (33–100%) was observed. Some patients had to interrupt mepolizumab due to lack of effectiveness or safety issues. Observed adverse events (0–55%) were mostly headache, respiratory tract infections, flu-like symptoms, and arthralgia.[14–20] The results of these studies are similar to ours; however, they are all limited by the small sample size, with a median of 12 (9–26) patients each.

Other studies carried out in other countries have also evaluated mepolizumab in real-life conditions. Pelaia and colleagues developed a single-centre observational study including 14 patients with severe and OCS-dependent eosinophilic asthma. All patients showed a sharp reduction of the frequency and severity of asthma exacerbations and 11 patients interrupted OCS (the remaining three patients also decreased their daily OCS dosage). Regarding adverse events possibly caused by mepolizumab, only a very mild irritation at the injection point was reported.[21]

Other authors have studied dropout rates in patients receiving mepolizumab in daily practice as an indirect reflection of its safety and tolerability. Lombardi and colleagues found a discontinuation rate of 4.2% (6 patients: 2 female and 4 male). The reasons were lack of response (five patients) and adverse events probably related to treatment (one patient).[22] In comparison with our study, we observed a greater dropout rate (13%).

Subjective parameters were also evaluated in our study, and 83% of the patients perceived improvement of the quality of life measured with the ACT.

Owing to the low prevalence of SREA, the main limitation of our study was its small sample size. In addition, the spirometry was not requested at a specific time of the treatment; therefore, pulmonary function could not be monitored in every patient.

It is also important to explain in detail the prescription criteria that have been applied into this study. In our country, the Spanish Agency of Medicines and Medical Devices is the regulatory agency that guarantees the efficacy, safety, and quality of pharmaceuticals and medical devices. Their functions include elaboration and publication of drugs' Therapeutic Positioning Reports, in which it summarizes efficacy and safety and establishes usage criteria, taking also into account a pharmacoeconomic perspective.

The Therapeutic Positioning Report of mepolizumab prioritizes its use in patients with SREA and an eosinophil count ≥500 cells/μL.

If the eosinophil count is <500 cells/µL, the prescription of mepolizumab has to be assessed individually, considering the severity of exacerbations and their treatment in the last year.[8]

These criteria are substantially different from those established by other national health services; for example, the NHS states that the most appropriate population should present a blood eosinophil count ≥300 cells/µL in the prior 12 months (with a history of exacerbations and/or dependence on systemic corticosteroids).[23]

The decision adopted by the Therapeutic Positioning Report was based on a subgroup analysis of the combined analysis of studies DREAM and MENSA, in which the greatest reduction (73%) in the frequency of severe exacerbations was observed in patients with baseline blood eosinophils ≥500/µL.

This prescription criterion has been established in our country to evaluate every new treatment with mepolizumab and, therefore, is the one that was considered in this study. Despite being more restrictive, it is not expected to influence in the results. However, it could be considered as another reason to explain the small sample size in spite of the inclusion of patients belonging to three different hospitals.

At the moment, mepolizumab entails an increased cost for the treatment of asthma. However, if exacerbations and the use of OCS are diminished, then chronic complications, healthcare costs, and other indirect costs will be diminished as well and treatment with mepolizumab could be an investment. An observational prospective study should be developed to obtain a pharmacoeconomic perspective.

Furthermore, many patients with SREA have also elevated IgE blood count and are candidates to receive omalizumab as well. Omalizumab has been commercialized in Spain since 2009 and almost half of the patients in our study (40%) were previously treated with this drug.

The benefit of switching patients with elevated IgE and eosinophil count, currently in treatment with omalizumab and not obtaining a satisfactory response, to mepolizumab should be evaluated in further studies.

In the pivotal trials[11–13] and the studies of other hospitals,[14–22] most of the patients receiving mepolizumab are women, and this was the same in our study. In addition, both patients in our study who abandoned the treatment due to lack of effectiveness were men. There are no studies evaluating the association with a susceptible subgroup and better clinical outcomes.

At the moment, there is no specialized pharmaceutical care for outpatients with asthma in the hospitals of Spain. We could not find studies evaluating the possible benefits of a specific program of pharmaceutical care for asthmatic patients in the clinical outcomes, or the adherence to the entire treatment, given that it is estimated to be under 50%.[1,2] Therefore, more studies are needed to evaluate the benefit that pharmacists can provide.

Article URL: https://www.drugsincontext.com/effectiveness-and-safety-of-mepolizumab-in-severe-refractory-eosinophilic-asthma:-results-in-clinical-practice/

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