Clinical Experience in the Treatment of Severe Eosinophilic Asthma With Mepolizumab

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Keywords: Real life, Interleukin-5, Eosinophils, Monoclonal antibodies, oral corticoids

ABSTRACT

Introduction: Severe eosinophilic asthma is an incapacitating disease requiring the patient to take many drugs, amongst which are oral corticoids (OCS), for its control. Mepolizumab is a monoclonal antibody capable of blocking the binding of Interleukin 5 (IL-5) to the eosinophils, and, in this way reducing the exacerbations, symptoms and need for OCS. Our objective was to evaluate the experience with this drug on patients being treated for severe asthma in real-life conditions.

Methods: Retrospective, multicentric study carried out in eight hospitals in the Principality of Asturias, in which the demographic, clinical, analytical, lung function and ACT (Asthma Control Questionnaire) data of the patients with severe eosinophilic asthma being treated with Mepolizumab for three years were collected.

Results: Sixty-nine patients (72% women) were included, with a mean age of 56±13 years. The eosinophil blood count before treatment was 856 cels/mm^3 (SD 754), decreasing after 6 months to 101 cels/mm^3 (SD 98). Annual exacerbations decreased from 4.7 (SD 3.7) to 1.3 (SD 2.5) (p=0.001), while the FEV1% increased from 68% (SD 20) to 76% (SD 21) (<0.001). At the onset 25 patients (36%) were using OCS (18 mg/day of prednisone) and after treatment this decreased to 13 (19%) (9mg/day of prednisone) (p=0.000), with complete withdrawal in 12 (48%). The response to Mepolizumab was positive in 56 patients (81%), and no adverse effects were observed.

Conclusions: Mepolizumab has demonstrated to be efficacious and safe in real life in the treatment of patients with badly controlled eosinophilic asthma.

Keywords: Real life, Interleukin-5, Eosinophils, Monoclonal antibodies, oral corticoids

INTRODUCTION

Asthma is a chronic respiratory disease characterised by the presence of inflammation, generally of an eosinophilic type, variable obstruction of the airways and bronchial hyperresponsiveness (1). Conventional treatment of asthma basically includes the use of corticosteroids and beta-2 agonists, although sometimes the severity of the process and the recurrence of exacerbations requires the addition of other drugs and the use of oral corticosteroids (OCS) (2). In some patients, with high levels of eosinophils in blood and sputum, the use of a drug (Mepolizumab) is indicated whose function is to block interleukin 5 (IL-5), and, in this way, avoid the mobility and the passage of the eosinophils towards the airways (3,4). The experience with Mepolizumab comes from diverse published clinical trials (5-9) as well as the clinical use in different countries (10,11). The drug has demonstrated efficacy in reducing exacerbations and the need for OCS, and also in improving the health-related quality of life (HRQoL) (12,13).

Three years after the introduction of Mepolizumab into our Autonomous Community, the objective was to describe the accumulated real-life clinical experience of the drug, and thus contribute relevant information in the treatment of severe asthma of an eosinophilic type.

MATERIAL AND METHODS

This is a descriptive, multicentric study, with data collected from the normal clinical practice of eight participating hospital Pulmonary medicine and Allergology departments in the Principality of Asturias, which represent the eight health care areas in which the community is divided and in total cover approximately 1,050,000 inhabitants. Each hospital collected the data of all the patients older than 14 years old diagnosed with severe eosinophilic asthma based on the criteria of ERS/ATS (2), uncontrolled despite the optimization of treatment, and that had been or were under treatment with Mepolizumab. In all the cases the drug was prescribed

according to the European Medicine Agency criteria (14) (> 150 eosinophils/ μL at the moment of treatment onset or at least a determination > 300 eosinophil/ μL in the last year). Patients treated from 1st January 2016 to 31st March 2019 were included. After the appropriate request from the Pharmacy Department, the drug was administered in each hospital at a dosage of 100mg each 4 weeks, by means of subcutaneous injection.

The following data were collected: demographic, clinical, analytical, prior treatment with Omalizumab, lung function, ACT (Asthma Control Test) as well as clinical evolution. All the patients were seen at least once in the first 6 months after treatment onset. We analysed the rate of exacerbations and hospitalizations in patients who were followed up for more than a year. A patient was considered responsive if they presented at least two of the following criteria: reduction of 50% of exacerbations, clinical significative reduction in OCS dosage or improvement of at least 3 points in the ACT score.

All patients were asked for an informed consent, which was read in the same way for all subjects. The information collected was entered into a database where those data related to identification were deleted to ensure their anonymity.

For data analysis, the quantitative variables were expressed as mean and standard deviation (SD) and the qualitative variables in percentage. For the study of the quantitative variables the t-Student test was used. The qualitative variables were analysed by means of the Chi-squared Pearson, applying Fisher's exact test when the frequency was less than 5. In all cases, the statistical significance was established at a value of $p<0.05$. The statistical analysis was carried out with the Stata v15.4.2 software.

RESULTS

A total of 69 patients (72% women) were included, all diagnosed with badly controlled severe eosinophilic asthma and a mean age of 56 ± 13 years. 18% of the total presented with a

previous clinical history of smoking but no patient was smoking at treatment onset. No statistically significant differences were observed in terms of sex, age or smoking history.

Table 1 shows the most common comorbidities, with the most frequent being rhinitis, presence of atopia, nasal polyposis or gastroesophageal reflux disease (GERD).

Twenty-four patients (35%) who had previously been treated with Omalizumab were withdrawn due to lack of improvement. From this group, 66% presented a positive response to Mepolizumab. No statistically significant differences were observed between the groups in response to Mepolizumab ($p<0.059$). Table 2 shows the differences observed in the needs of rescue bronchodilator medication, the ACT, the number of exacerbations a year, lung function, and patients with OCS before and after treatment with Mepolizumab.

Daily use of the short acting Beta-2 agonists as rescue showed a significant decrease after treatment onset (75% vs. 29%). The score in the ACT significantly improved from 13.2 points (SD 4.4) to 17.5 points (SD 4.8). The rate of exacerbations per year decreased from 4.7 (SD 3.7) to 1.3 (SD 2.5); a reduction of 72%. In this way, an improvement in the lung function of the treated patients was observed, with an increase of FEV1% from 68% (SD 20) to 76% (Sd 21).

At the onset the total number of patients treated with daily OCS was 25 (36%), with an average dosage of prednisone of 18mg/day (SD14.2). After treatment with Mepolizumab, the number of patients needing OCS decreased to 13 patients (19%) with the prednisone dose decreasing to 9mg/day (SD 10.9), and in 12 (48%) patients taking these drugs daily it was possible to completely remove them. In 11 patients (44%) it was possible to reduce the daily dose and in 2 patients (8%) it was impossible to do so. In the patients with a reduced dose of OCS, a global decrease of 50% with respect to the initial figure was achieved.

The total number of eosinophils in blood at basal situation was 856 cels/mm^3 (SD 754) and after treatment it decreased to 101 (SD 98). In the case of the patients considered as

responsive, the initial figure was 812 cels/mm^3 (SD 194) at onset decreasing to 42 cels/mm^3 (SD 34) after starting treatment.

The response to Mepolizumab was considered positive in 56 patients (81%), while in 13 (19%) treatment was removed for lack of response. In two cases considered responsive (3%), treatment was removed due to secondary effects.

Secondary effects were objectified in 7.2% of the patients (table 3), of which the most frequent was athromyalgia (3 patients) followed by skin rashes at the injection site (1 patient) and headaches (1 patient). Among the patients suffering from adverse effects the treatment had to be withdrawn in two cases due to arthromyalgia non-responding to analgesics.

In the univariant analysis no statistically significant positive predictors were found in response to Mepolizumab except for the presence of blood eosinophilia ($p=0.002$).

DISCUSSION

This work presents the real-life clinical experience in our Autonomous Community after 3 years using Mepolizumab as treatment for severe eosinophilic asthma. The results show a clear improvement for the patients, which is reflected in a reduction of the number of exacerbations, improved clinical control, and a reduction in the use of OCS. The data are very similar to those in the literature, both in the controlled clinical trials (5-9) and in the real-life studies carried out with the drug (11,15-18). In this way, the type of patients included in our series are very similar to those already published, both in existence of associated comorbidities and in the presence of secondary effects attributed to the administration of the drug.

On evaluating the control of asthma in patients treated with Mepolizumab, we can find a significant statistical improvement in the increase of the ACT score. In the MENSA study (5) a significant improvement in the control of asthma in the ACT of -0.44 ($p<0.001$) was observed, and an improvement of the ACT of -0.4. in the MUSCA (9) existed. The DREAM

study differs (7), where a treatment dose of 75mg iv shows no statistically significant differences vs. placebo in terms of asthma control (ACQ). If we analyse the real-life studies that the ACT used as control tool for asthma, Bagnasco et al. (11) found an improvement of 5 points and Montero Perez et al. (15) of 7.3 points in the questionnaire. This shows that, similarly to our study, the treatment of Mepolizumab improves the clinical control of the patients.

On observing the lung function of our patients, it was seen that after 6 months of treatment the FEV1 had improved on average by 177ml, with this increase being statistically significant. Moreover, the FEV1 increment in diverse studies published in the literature is normally relatively modest. In the study by Ortega et al. (5) the postbronchodilator FEV1 showed an increase of 138ml, greater in patients receiving Mepolizumab subcutaneously than in those on placebo. However, in the study by Chupp et al. (9), the prebronchodilator FEV1 showed an improvement of 120 ml greater in the Mepolizumab with respect to the placebo group, while with the postbronchodilator FEV1, the FEV1 improvement was similar in both groups. This contrasts with Bagnasco et al. (11), where the FEV1 improvement after Mepolizumab treatment was 340ml at 12 months. On analysing the improvement in the FEV1 %, in our study it increased from 68% to 76%, which is similar to that noted by Sposato et al. (72 to 78%) (17). Even though improvement in lung function was not one of our objectives when the drug was prescribed, we did observe that the real-life results tended to be better than the clinical trial results, which can also lead to an improvement in the control of the disease.

On analysing the OCS treatment, in our study we can see a significant decrease in the need for daily OCS in those patients who could not be completely taken off treatment (18mg of prednisone to 9mg); both in the number of patients (withdrawn in 48% and dose reduced in 44%) as well as the daily dose. Thus, from our experience the results are more favourable than those from the SIRIUS study (6), where 235 of the patients treated with Mepolizumab

experienced a reduction of 90-100% of dose in the use of OCS with respect to placebo (11%), and 64% experienced some degree of reduction in the daily dose of OCS. In the Sposato et al. study (17), where they retrospectively included 134 asthma patients treated with Mepolizumab, the OCS were withdrawn in 45.6% of the patients, with similar values to those observed in our study. These figures are slightly higher in the study by Caminati et al. (18) where OCS were removed in 56% of the patients. The withdrawal or reduction of OCS is one of the main objectives in the treatment of asthmatic patients in advanced stages. As this objective can be reached with Mepolizumab it is extremely important since the undesired effects of OCS imply high levels of morbimortality, whose handling is extremely expensive.

In our series, only 15% of those treated with Mepolizumab had to be withdrawn at 6 months due to a lack of improvement, while in the SIRIUS study that percentage was 36%. In the study by Montero Perez et al. the figure of the non-responders was 13% (15), which is relatively similar to ours. A positive response of 81% in a drug without doubt is a good response and makes Mepolizumab an effective drug for the treatment of severe eosinophilic asthma.

In the univariant analysis no statistical significance for any variable that could be considered a good response predictor to Mepolizumab was found except for the presence of blood eosinophils. This is perhaps due to the low number of patients analysed or to the loss of some data, given that it is a retrospective study.

Tolerance to the drug was very good. Only two patients presented adverse effects leading them to treatment withdrawal, which consisted of arthralgias that did not respond to the analgesic treatment. In the DREAM study (7) it was concluded that Mepolizumab is a well-tolerated drug, with headaches and nasopharyngitis being the most frequently described secondary effects. In the SIRIUS study the most frequent adverse effects were headaches (20% with Mepolizumab vs. 21% with placebo) and nasopharyngitis (14% with Mepolizumab vs. 15% with placebo). Also, seven patients (4 with Mepolizumab vs. 3 with placebo) had systemic

reactions, and six patients (4 with Mepolizumab vs. 2 with placebo) had local reactions at the injection site. In the COSMOS study, only one patient presented serious adverse effects in relation with a hypersensitivity Type IV reaction and in the COSMEX (extension of anterior) similar data were demonstrated (19). No reaction of anaphylaxis after administration was observed. Thus, in the literature, and similar to our study, it was observed that Mepolizumab is a drug that can be safely administered as the secondary effects in general are few and slight.

One of the main limitations of the study is the fact that it is retrospective. However, the data was collected with the same protocol and it was a real-life study, the data belonged to eight different hospitals and the treatment onset criteria was regularly revised and agreed upon by the authors. The advantages of clinical trials in terms of statistical goodness of fit should be contrasted with those obtained in real life, which reflects the normal working manner of each health centre.

CONCLUSIONS

Our experience with the use of Mepolizumab in the treatment of severe eosinophilic asthma shows a clear improvement in clinical control, a significant reduction in exacerbations and especially in the daily dose of OCS. And this needs to be considered alongside the scarce secondary effects attributable to the drug. The next years, with a wider accumulated experience in the use of the drug, should give us greater information on the impact of this type of biological treatment in asthma.

CONFLICT OF INTERESTS

No conflicts of interest exist.

DECLARATIONS

Ethics approval and consent to participate

- The ethics committee of the Principality of Asturias has approved the project with the number 2020.417

Consent for publication

- Not applicable

Availability of data and materials

- Not applicable

Competing interests

- The authors declare that they have no competing interests

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Authors contributions

- Enríquez A.I. and Hermida T. collected data from patients included by their hospital and they were the major contributors in writing the manuscript
- Romero P., Gullón J.A., Expósito A.R., Escobar M.J., Beristain A., Alonso M.A., Gutiérrez M., Castaño G., Jiménez J. and Fernández R. collected data from patients included by their hospital
- López F.J. contributed to the statistical study
- García Clemente M. and Casan P. were the major contributors in reading and correcting the manuscript
- All authors read and approved the final manuscript

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Table 1: Comorbidities in patients treated with Mepolizumab

Clinical features	Number of patients (%)
Rhinitis	50 (72.5)
Atopy	36 (52.2)
nasal polyposis	32 (46.4)
GERD	25 (36.2)
Anxiety-depressive disorder	23 (33.3)
Obesity	19 (27.5)
Bronchiectasis	17 (24.6)
Intolerance to NSAIDs	11 (15.9)
Churg Strauss syndrome	6 (8.7)

Table 2. Main features of patients pre and post treatment with Mepolizumab

Variables	Pre mepolizumab (n=69)	Post mepolizumab (n=69)	p
SABA daily (nº (%))	52 (75%)	20 (29%)	0.000*
ACT (score)	13.22	17.5	<0.001*
Exacerbations/year	4.7	1.3	0.001*
Hospital admissions/year	0.3	0.09	0.33
FEV1 (ml)	1883	2060	0.003*
FEV1 (%)	67.6	76.4	<0.001*
Oral corticosteroids (n)	25	13	0.000

Table 3: Adverse effects in the patient group grupo treated with Mepolizumab

Events	Number of patients (%)
Arthromyalgias	3 (4.3)
Skin rashes at injection site	1 (1.4)
Headaches	1 (1.4)