



REal world Effectiveness and Safety of Mepolizumab in a Multicentric Spanish Cohort of Asthma Patients Stratified by Eosinophils: The REDES Study

Christian Domingo Ribas^{1,2} · Teresa Carrillo Díaz^{3,4} · Marina Blanco Aparicio⁵ · Eva Martínez Moragón⁶ · David Banas Conejero⁷ · M. Guadalupe Sánchez Herrero⁷ on behalf of the REDES Study Group

Accepted: 20 August 2021

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Abstract

Background The efficacy of mepolizumab is well documented in severe eosinophilic asthma (SEA), although the stringent selection criteria adopted by SEA clinical trials limits the generalizability of results.

Objective Our study evaluated the effectiveness and safety of mepolizumab in patients with SEA in Spain. The primary efficacy endpoint was the change in the rate of clinically significant asthma exacerbations 12 months after starting mepolizumab compared to the baseline rate in the 12 months prior to treatment. Patients were stratified by baseline blood eosinophil counts.

Methods We conducted a multicentric observational cohort study of SEA patients treated with mepolizumab across 24 specialized hospital asthma units in Spain. Severe exacerbation rate, lung function, oral corticosteroid use (OCS) and asthma control test (ACT) were retrospectively collected and compared during the 12-month pre- and post-mepolizumab treatment. Adverse events were also investigated.

Results A total of 318 patients with SEA were included (mean age: 56.6 years, 69.2% female). Exacerbation rates decreased by 77.5%, and 50.6% of patients did not suffer any exacerbations during the 12 months of treatment. The difference in forced expiratory volume in 1 s (FEV1) pre- and post-bronchodilator after starting mepolizumab was 0.21 (0.46) L (95% CI 0.14–0.27) ($p < 0.001$). Exacerbations and lung function significantly improved across all eosinophil subgroups. Among the 98 patients on OCS, 47.8% were able to discontinue this treatment and the mean daily dose was decreased by 59.9%. The baseline ACT score was 14.1, increasing by a mean (SD) of 6.7 points (1.9) at 12 months. Adverse events related to mepolizumab were uncommon.

Conclusions This real-world study of SEA patients confirms that mepolizumab is effective in reducing clinically meaningful exacerbations, improving lung function, and decreasing OCS dependence and mean OCS dose at 12 months, irrespective of baseline eosinophil counts.

The members of “on behalf of the REDES Study group” is present in the Acknowledgements section.

✉ Christian Domingo Ribas
cdomingo@tauli.cat

Extended author information available on the last page of the article

Key Points

Pivotal studies and post hoc analyses of these studies have shown that mepolizumab is effective at eosinophil values of 150 cells/ μ L and above. Whether these benefits are also maintained in real life is of interest.

REDES is a real-life study performed in Spain that evaluated the effectiveness and safety of mepolizumab in severe eosinophilic asthma that incorporates a prespecified stratification by blood eosinophil counts for outcomes analysis.

Mepolizumab reduced severe exacerbations and oral corticosteroid consumption, and improved asthma control. These benefits occurred irrespective of baseline eosinophil counts.

No severe adverse events related to mepolizumab were reported.

1 Introduction

Severe asthma encompasses a heterogeneous group of patients, with an estimated prevalence of 7.7% among individuals with asthma [1], which implies a substantial use of healthcare resources. There is an increasing consensus that the control of severe asthma is a major unmet need. The ERS/ATS task force defines severe asthma as a disease that, after asthma diagnosis is confirmed and co-morbidities addressed, requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy [2–4].

Knowledge of the pathophysiology of severe asthma has improved during the last decade, and significant contributions on characterizing phenotypes have emerged from severe asthma cohorts and patient registries [5–7]. Adequate identification and management of these patients is key to preventing disease exacerbations and improving health-related quality of life. In this sense, the identification of eosinophilic asthma patients, which represent most of the type 2 asthma patients, is undoubtedly an increasingly relevant aspect of the asthma therapeutic approach [5, 8].

Mepolizumab, the first approved anti-IL-5 monoclonal antibody, binds to and blocks IL-5, a key factor in the regulation of the growth, differentiation, activation and survival of eosinophils. Several clinical trials have shown its efficacy in reducing exacerbations (MENSA) and oral corticosteroid use

(OCS) (SIRIUS), and improvement in quality of life (QoL), asthma control and lung function (MUSCA) [9–11]. It has also been shown to be effective as an alternative therapy for a group of patients not optimally controlled on omalizumab (OSMO) [12]. However, whilst the efficacy of mepolizumab is well documented, real-life data from independent sources on its effectiveness are currently limited, although growing through case series and global cohorts [13, 14]. However, several single-centre real-life studies have shown evidence of the effectiveness of mepolizumab [15–18]. Moreover, the stringent selection criteria adopted by clinical trials in general and by monoclonal antibody development programs in severe asthma are highly restrictive [19].

The threshold of peripheral blood eosinophils at which anti-IL5 drugs are effective has been widely discussed in the literature. On the other hand, it has also been postulated that the lower the peripheral blood eosinophil value achieved by biological treatment, the better the clinical outcome. Pivotal studies and post hoc analyses of these studies show that mepolizumab is effective at eosinophil values of 150 cells/ μ L and above. Whether these benefits are also maintained in real life is of interest [9].

As a result, we conducted a study to comprehensively evaluate the REal-world Effectiveness and Safety of mepolizumab in severe eosinophilic asthma (SEA), the REDES study. REDES incorporates two aspects: a prespecified stratification by blood eosinophil counts for outcomes analysis, and the fact that it has been performed in a Southern European patient population.

2 Methods

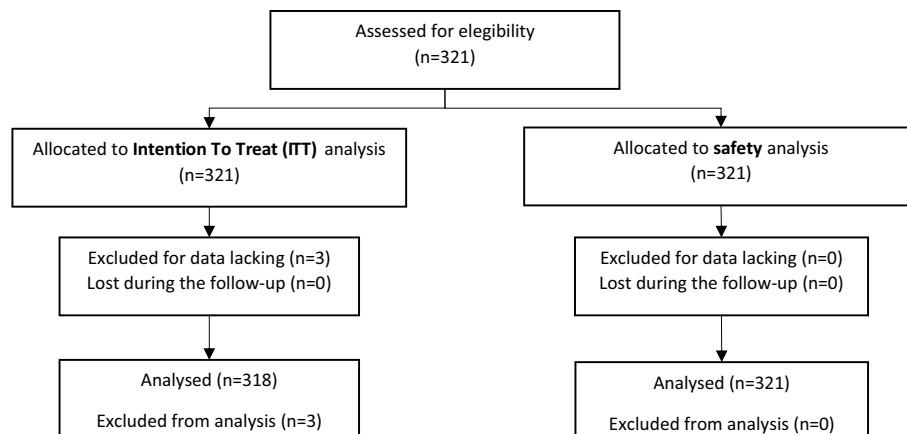
2.1 Design and Study Population

We conducted a phase IV, multicentric observational cohort study of severe eosinophilic asthma patients treated with mepolizumab across 24 geographically distributed Asthma Units in Spain. Sites were selected using a standard feasibility questionnaire ensuring they met the minimum relevant criteria for the study endpoints and geographic representativeness. Investigators needed to have followed up severe asthma patients regularly (i.e., every 6 months) for 12 months before mepolizumab initiation and at least 12 months after that date.

Investigators consecutively enrolled all eligible patients who met the inclusion criteria (Online Supplementary Material (OSM), Fig. 1). Data were retrospectively collected from patients' clinical records between December 2019 and July 2020 over an 8-month period.

Key inclusion criteria were a diagnosis of severe eosinophilic asthma in individuals aged ≥ 18 years, with at least 12 months since the start of mepolizumab treatment, regardless

Fig. 1 Patient flowchart



of their treatment continuation at data inclusion time, with a regular follow-up since treatment initiation (at least every 6 months), and the availability of continuous follow-up information in the 12 months before the introduction of mepolizumab. The key exclusion criteria were participation in an interventional asthma study in the 12 months prior or after initiating mepolizumab and missing key clinical information to define the primary endpoint.

2.2 Outcome

The primary outcome was the annual rate of clinically significant asthma exacerbations. These were defined as those exacerbations requiring the administration of a systemic corticosteroid for at least 3 days (or doubling the dose in patients on maintenance OCS), or if the patient had visited an emergency department or was hospitalized. Exacerbation rates in the 12 months before and after mepolizumab initiation were compared, and the percentage of reduction was calculated. For patients who discontinued treatment before the 6-month or 12-month timepoint, their last available measurement during treatment was used for the endpoint analyses. Two stratifications were carried out to baseline eosinophil levels: by ranges (< 150 eosinophils/ μL , ≥ 150 and $< 300/\mu\text{L}$ and ≥ 300 and < 500 eosinophils/ μL at treatment initiation) and by lower thresholds: ≥ 150 eosinophils/ μL , ≥ 300 eosinophils/ μL , ≥ 500 eosinophils/ μL and ≥ 700 eosinophils/ μL at treatment initiation).

2.3 Study Measurements

Secondary outcomes included pre- and post-bronchodilator spirometric tests, compared at 6 months and 12 months after mepolizumab treatment to baseline values, changes in the number of eosinophils pre-/post-treatment were also assessed. In patients receiving a maintenance OCS dose at the time of mepolizumab initiation, changes in the average OCS daily maintenance dose were calculated

pre-/post-mepolizumab treatment. Symptom control was assessed using the Asthma Control Test (ACT) at baseline, at 6 months, and at 12 months after treatment initiation. Scores at 6 months and 12 months after mepolizumab treatment were compared to baseline.

We investigated the effect of baseline eosinophil count on exacerbations, ACT, and lung function following mepolizumab treatment. For this, patients were grouped according to their baseline blood eosinophil counts (≥ 150 cells/ μL , ≥ 300 cells/ μL , ≥ 500 cells/ μL and ≥ 750 cells/ μL), and baseline blood eosinophil ranges (< 150 cells/ μL , 150–299 cells/ μL , 300–499 cells/ μL , 500–699 cells/ μL and ≥ 700 cells/ μL).

Safety was assessed by the collection and description of drug-related adverse events (AEs) during the study. The investigators determined the relationship of the AE to mepolizumab.

2.4 Sample Population Size Calculation

The study sample size was calculated according to the primary objective, the change in the number of exacerbations. A power analysis based on data from the COSMOS (MEA115661) open-label 1-year extension study was used to calculate the minimum sample size to measure a change in asthma exacerbation rate in real life. Patients on placebo during the MENSA study (MEA115588) experienced a 42% exacerbation reduction during COSMOS, from 1.9 exacerbations/year to 1.1 exacerbations/year. The power analysis considered a sample size of 350, after assuming an assumed 10% of missing data, meaning that we would need to include 320 patients. A one-sided test and $\alpha = 0.05$ showed that a sample of 320 patients had almost 100% power to detect the above-mentioned change in exacerbations.

2.5 Statistical Analysis

For the description of continuous variables, the mean (with 95% CI), median, standard deviation (SD), interquartile range (IQR), minimum and maximum values were used. For the description of categorical variables, number and percentage within categories with 95% confidence intervals (CIs) were calculated. A paired two-tailed *t*-test was used for comparison of before/after periods for continuous variables and the McNemar test for categorical variables. To compare more than two groups, ANOVA was used. Exacerbation rates were modelled using a Poisson model, adjusted for treatment duration. A statistical significance level of 0.05 was used. All analyses were done using SAS version 9.2.

3 Results

3.1 Overall Baseline Characteristics

In total, 321 patients were enrolled, and 318 patients were eligible for the study. Three patients were excluded due to incomplete information on the study primary endpoint. There were no losses to follow up. The mean (SD) age of the population was 56.5 (12.5) years. The gender distribution showed a predominance of women ($n = 220$, 69.2%) (Table 1). The mean (SD) body mass index (BMI) was 28.6 kg/m² (5.50), and 72.8% of patients ($n = 230$) were overweight, obese or severely obese. Nasal polyposis was present in 147 patients (46.2%), and allergic asthma was present in 193 patients (60.7%). The diagnosis of allergic asthma was clinical and not always supported by allergy testing. Atopic sensitization was recorded in 131 patients, of which dust mites were the most common (53.9% prick test and 45.3% specific IgE). Daily OCS maintenance therapy was used by 98 patients (30.8%), and the mean (SD) dose was 12.1 mg/day (10.0). Most patients (84.9%, $n = 237$) had poor asthma control at baseline (ACT score < 20). Of the patients included in the study, 91.8% presented some co-morbidity, the most frequent being nasal polyposis (46.2%), followed by chronic rhinosinusitis (24.2%) and gastroesophageal reflux disease (GERD) (21.2%). Allergic rhinitis was recorded in 21.7% of the cases (Table 1).

3.2 Previous Treatment

A total of 121 (38.2%) of the patients were previously treated with omalizumab, and all of them switched to another biologic treatment due in most cases to a lack of effectiveness or inadequate control (95; 78.5%) (Table 1).

At the time of the study visit, the mean duration of mepolizumab to discontinuation or to the date of the baseline visit (censored data) was 2.2 years. Two hundred and

Table 1 Baseline overall characteristics of patients

Baseline characteristics	$n = 318$
Age mean (SD)	56.6 (12.5)
Age at asthma diagnosis (years), mean (SD)	34.1 (17.9)
Sex	
Female	220 (69.2%)
Ethnicity	
Caucasian	283 (89.0%)
BMI (kg/m ²), mean (SD)	28.59 (5.50)
< 18.5	2 (0.6%)
18.5–25	84 (26.6%)
25–30	122 (38.6%)
30–35	72 (22.8%)
> 35	36 (11.4%)
Blood eosinophil count (cell/μL), mean (SD)	710.2 (836.8)
Blood eosinophil count (cell/μL), median (IQR)	550.0 (360.0; 860.0)
< 150	25 (7.9%)
150–299	23 (7.3%)
300–499	84 (26.5%)
500–699	61 (19.2%)
≥ 700	124 (39.1%)
Smoking habits	
Never-smoker	198 (62.3%)
Ex-smoker (> 6 months)	106 (33.3%)
Smoker	4 (1.3%)
Passive	6 (1.9%)
Family history asthma	92 (31.9%)
ACT, mean (SD)	14.1 (5.0)
ACT not well controlled (ACT score < 20)	237 (84.9%)
OCS maintenance dose ($n = 98$), mean (SD)	12.1 (10.0)
Allergic asthma*	193 (60.7%)
Atopic sensitization**	131 (41.5%)
Positive cutaneous test	102 (32.1)
Pollen	44 (43.1%)
Animal epithelium	35 (34.3%)
Mites	55 (53.9%)
Positive specific IgE test	64 (20.1)
Pollen	32 (50.0%)
Animal epithelium	23 (35.9%)
Mites	29 (45.3%)
Previous omalizumab treatment	121 (38.2%)
Time on treatment, median (IQR)	24.0 (12.0; 48.0)
Discontinued due to inadequate control	95 (78.5%)
Co-morbidities	292 (91.8%)
GERD	67 (21.1%)
Chronic rhinosinusitis	77 (24.2%)
Allergic rhinitis	69 (21.7%)
Nasal polyposis	147 (46.2%)
Chronic rhinosinusitis and nasal polyposis	34 (10.7%)
Atopic dermatitis	4 (1.3%)
Hypersensitivity to NSAIDs	42 (13.2%)

Table 1 (continued)

Baseline characteristics	<i>n</i> = 318
Bronchiectasis	59 (18.6%)
Anxiety	62 (19.5%)
Depression	55 (17.3%)
EGPA	11 (3.5%)

Values are *n* (%) unless otherwise specified

BMI body mass index, *IgE* immunoglobulin E, *IQR* interquartile range, *SD* standard deviation, *EGPA* eosinophilic granulomatosis with polyangiitis, *OCS* oral corticosteroid, *GERD* gastroesophageal reflux disease, *NSAID* nonsteroidal anti-inflammatory drug, *ACT* asthma control test

*Allergic asthma = the diagnosis of allergic asthma was a clinical diagnosis and collected from the patient's medical history

**Atopic sensitization includes recording of IgE positivity or prick test positivity to food or airborne allergen

ninety-four (92.5%) of the patients continued to receive mepolizumab; three patients (0.9%) discontinued mepolizumab treatment 6 months, the main reason being inadequate control and adverse events (Table 2).

3.3 Exacerbations

For the primary endpoint, the number of exacerbations was significantly reduced by 77.5% during the year post-mepolizumab introduction ($p < 0.001$), which went from a mean (SD) of 4.5 (3.5) exacerbations per year during the pre-mepolizumab treatment period, to 1.0 (1.4) in the post-mepolizumab initiation period. All prespecified eosinophil subgroups reduced the mean number of exacerbations, irrespective of the eosinophil count (Fig. 2 and OSM Table 1). In the 12 months before mepolizumab treatment, a total of 91.8% ($n = 292$) of severe eosinophilic asthma patients had experienced an exacerbation. This proportion was significantly reduced to 49.4% ($n = 157$) in the post-mepolizumab period (p -value < 0.001), with 50.6% of patients experiencing no exacerbations during the 12 months post-initiation (OSM Table 2 and OSM Fig. 2).

Exacerbations that required an emergency department visit/hospitalization decreased by 79.4% from 1.6 (2.08) to 0.3 (0.8) (p -value < 0.001) (Fig. 3).

3.4 Lung Function

Figure 4 illustrates the evolution of the mean forced expiratory volume in 1 s (FEV1) pre- and post-bronchodilator use according to the different blood eosinophil subgroups. Overall, the mean FEV1 increased by 10.4% and a mean (SD) of 0.21 L (0.46) ($p < 0.001$). Changes in lung function in terms of the mean pre- and post-bronchodilator FEV1 are shown in OSM Table 3.

Table 2 Clinical characteristics at baseline (mepolizumab initiation)

Variable	Total
Continuation of mepolizumab treatment at study visit	
Valid <i>n</i>	318 (100%)
No	24 (7.5%)
Yes	294 (92.5%)
Time (days) on mepolizumab treatment	
Valid <i>n</i>	318
Mean (SD)	789.34 (413.86)
Median	728.5
(P25; P75)	(507.0; 952.0)
(Min; max)	(62.0; 2777.0)
Missing <i>n</i>	0
Time (years) on mepolizumab treatment	
Valid <i>n</i>	318
Mean (SD)	2.16 (1.13)
Median	2.0
(P25; P75)	(1.4; 2.6)
(Min; max)	(0.2; 7.6)
Missing <i>n</i>	0
Discontinuation of mepolizumab at 6 months	
Valid <i>n</i>	318 (100%)
No	315 (99.1%)
Yes	3 (0.9%)
Main reason for discontinuation at 6 months	
Valid <i>n</i>	3 (100%)
Adverse events	1 (33.3%)
Inadequate control	2 (66.7%)
Months on treatment before discontinuation	
Valid <i>n</i>	3
Mean (SD)	3.00 (1.73)
Median	2.0
(P25; P75)	(2.0; 5.0)
(Min; max)	(2.0; 5.0)
Switching to another biologic treatment	
Valid <i>n</i>	3 (100%)
Yes	3 (100%)
Biologic treatment for switching	
Valid <i>n</i>	3 (100%)
Benralizumab	2 (66.7%)
Benralizumab (also stopped due to side effects)	1 (33.3%)

Valid *n* number of valid patients included in the analysis

3.5 Oral Corticosteroid Reduction

A total of 98 patients required maintenance OCS treatment at baseline. Forty-three (47.8%) of these patients were able to discontinue OCS after 12 months (Fig. 5 and OSM Table 3), and the mean daily OCS maintenance dose decreased by 50.4% and 59.9% at 6 and 12 months, respectively, from 12.1 mg/day at baseline to 6 mg/day at month 6 and 4.9 mg/

Fig. 2 Mean number of total exacerbations 12 months pre- and post-mepolizumab initiation by baseline eosinophil subgroups and thresholds

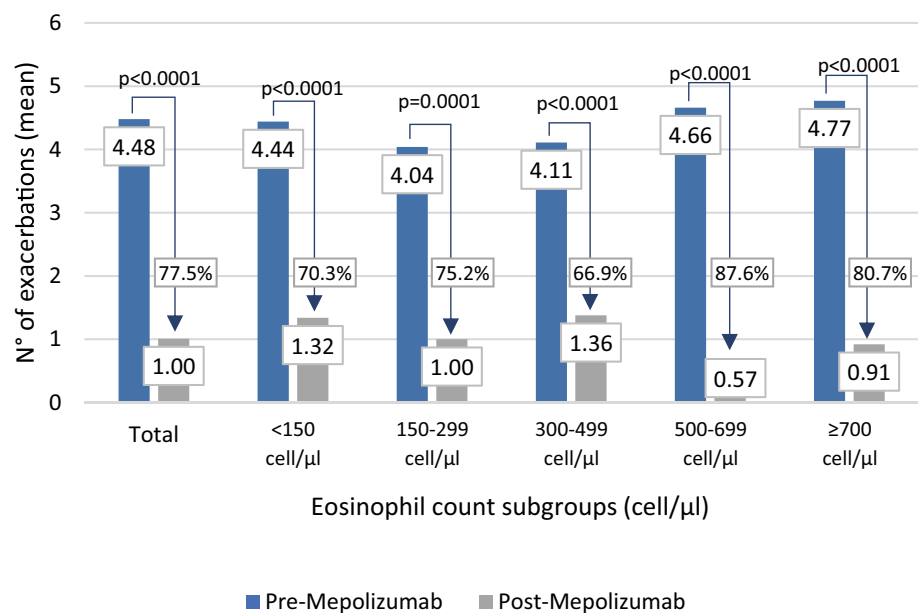
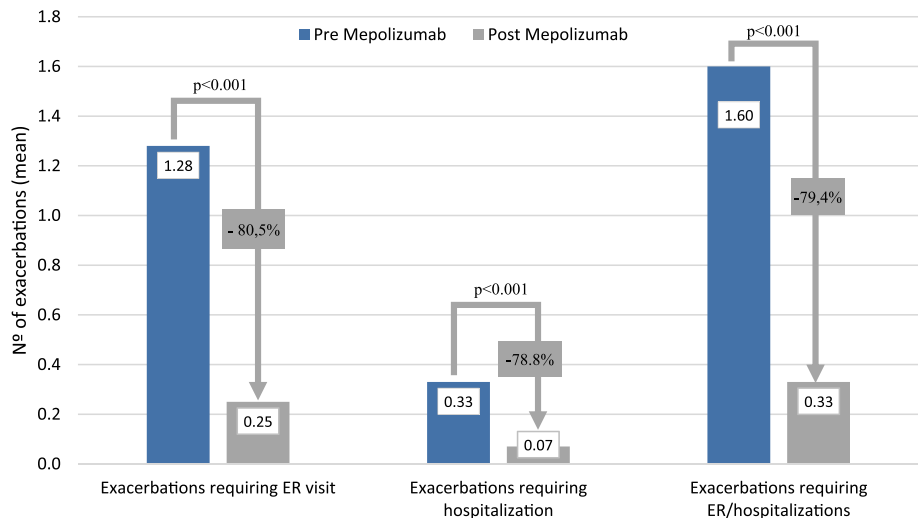


Fig. 3 Change in annual exacerbation rates pre- and post-mepolizumab initiation by exacerbation type. Three types of exacerbation types were considered: exacerbations requiring only corticosteroid, requiring emergency room (ER) visit and requiring hospitalization. Total exacerbations represent all exacerbations together, while exacerbations requiring ER/hospitalizations represent the sum of each individual category



day at month 12 (Fig. 5 and OSM Table 4). The baseline OCS maintenance dose was high (≥ 7.5 mg/day) in 57.1% of OCS-treated patients ($n = 56$) and decreased to 32.3% ($n = 30$) and 28.9% ($n = 26$) at 6 and 12 months, respectively.

3.6 Symptom Control

The ACT is a simple, patient-based, five-item tool for identifying patients with poorly controlled asthma, with a score that ranges between 5 and 25 [20]. A score ranging between 20 and 25 means that the patient is well controlled. A cut-off score of ≤ 19 indicates patients with poorly controlled asthma [21]. A score between 16 and 19 is considered partially controlled asthma; a score < 16 indicates the patient's asthma is uncontrolled. The minimally important difference (MID) for the ACT was established at three points [22].

The mean (SD) ACT score at baseline was 14.1 (5.0) and increased by a mean (SD) of 6.1 and 6.7 (1.9) points after 6 and 12 months of follow-up, reaching a final score of 20.3 and 20.8, respectively. In 78.3% of patients, the pre-post difference was at least 3 points ($p < 0.001$) (Fig. 6 and OSM Table 4).

3.7 Blood Eosinophil Counts

The population treated with mepolizumab in Spain was highly eosinophilic, with 39.3% of the study sample having values over 700 cells/ μ L. The overall mean (SD) baseline eosinophil count was 710.16 cells/ μ L (836.82), and treatment with mepolizumab reduced this to a mean (SD) of 124.74 (457.74) cells/ μ L ($p < 0.001$) at 12 months, representing an 82.4% reduction.

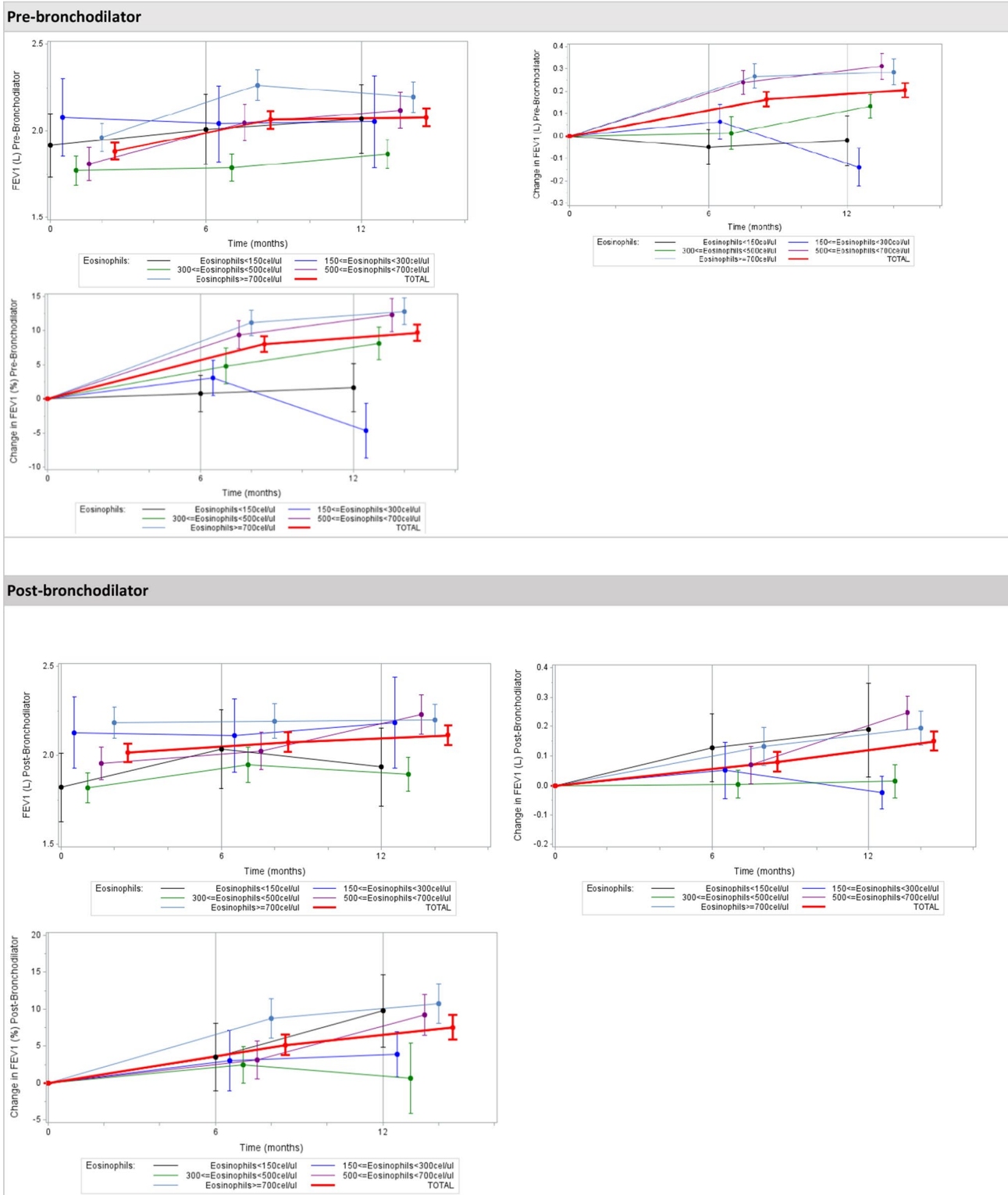


Fig. 4 Mean and standard error for evolution of forced expiratory volume in 1 s (FEV1) pre- and post-bronchodilator use according to baseline eosinophil level. FEV1 before and after bronchodilators is

expressed in (L) and as a percentage (%). The change in FEV1 represents the mean difference from baseline at 6 and 12 months

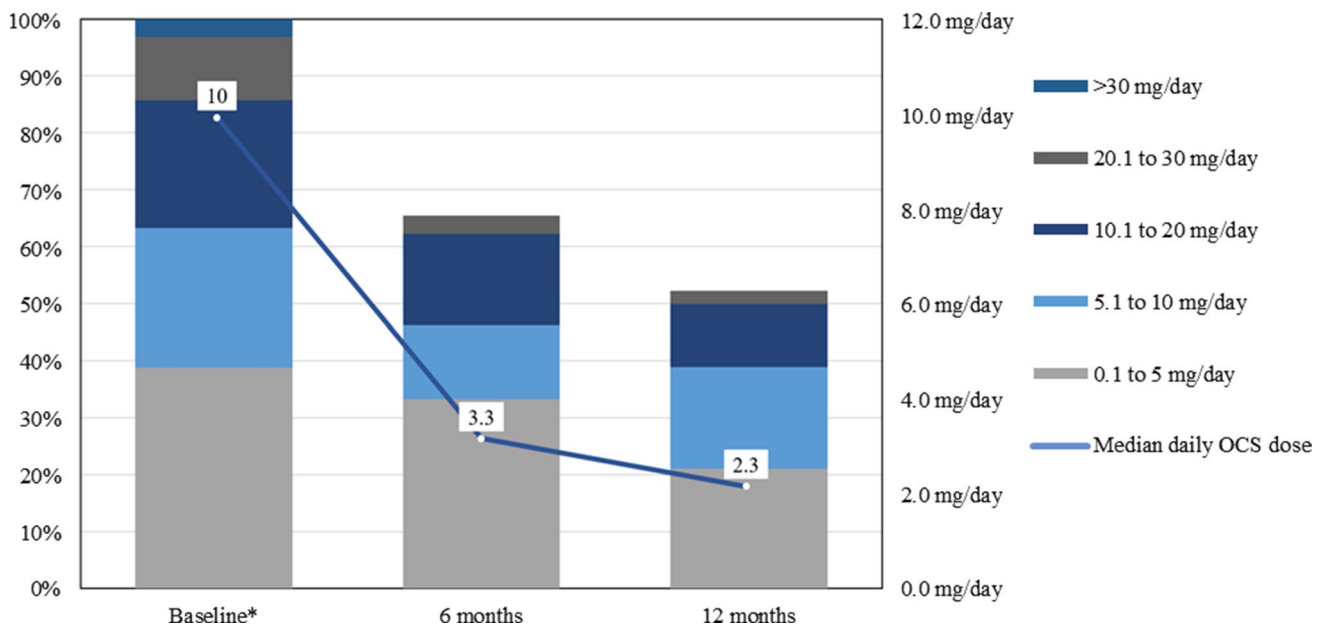


Fig. 5 Daily dose evolution of oral corticosteroid use (OCS; ranges and median daily dose of prednisone equivalent) in patients with maintenance corticosteroids at baseline. The left Y-axis represents the total percentages, which are based on the total number of patients with OCS treatment at baseline ($n = 98$). The right Y-axis represents

the median OCS dose progression. The X-axis represents the three different assessment time points (baseline, 6 and 12 months). The colour gradients represent the OCS dose ranges, where the volume represents the percentage of patients within each range

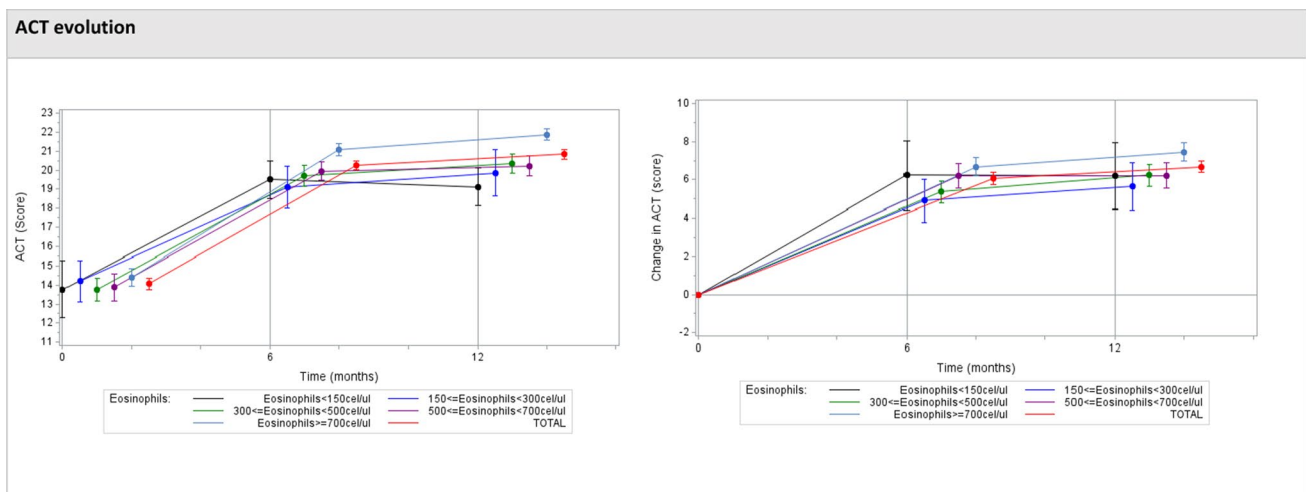


Fig. 6 Evolution from baseline in Asthma Control Test (ACT) scores after mepolizumab initiation. Evolution and change in the mean ACT scores over the three different assessment time-points (baseline, 6 and

12 months) according to blood eosinophil counts at baseline. ACT score > 19 indicates well-controlled asthma

3.8 Safety

During the study period, nine patients (2.8%) out of the 321 registered AEs related to mepolizumab, reporting a total of 13 AEs related to mepolizumab (Table 3). The incidence of musculoskeletal and connective tissue disorders related to

mepolizumab was 1.6%. No severe AEs related to mepolizumab were reported.

The mean duration of mepolizumab until interruption or the date of data inclusion (whichever occurred first) was 2.2 years. At 6 months only three patients (0.9%) had discontinued mepolizumab due to inadequate control ($n = 2$) and AEs ($n = 1$). Treatment persistence was 98.1% ($n = 312$)

Table 3 Adverse drug-related events

	<i>n</i> (%)
Overall	
Patients with adverse events related to mepolizumab*	9 (2.8%)
MedDRA Term* for adverse events	
Musculoskeletal and connective tissue disorders	5 (1.6%)
Arthralgia	1 (0.3%)
Arthromyalgia	2 (0.6%)
Bone pain	1 (0.3%)
Myalgia	1 (0.3%)
Nervous system disorders	2 (0.6%)
Headache	2 (0.6%)
Skin and subcutaneous tissue disorders	2 (0.6%)
Acneiform dermatitis	1 (0.3%)
Skin xerosis	1 (0.3%)
Gastrointestinal disorders	1 (0.3%)
Diarrhoea	1 (0.3%)
General disorders and administration site conditions	1 (0.3%)
Febricula	1 (0.3%)
Injury, poisoning and procedural complications	1 (0.3%)
Procedural headache	1 (0.3%)
Vascular disorders	1 (0.3%)
Deep vein thrombosis	1 (0.3%)

Table percentages are based on the total population (*n* = 318)

MedDRA Medical Dictionary for Regulatory Activities

*Investigator’s criteria

at 12 months after mepolizumab initiation, and no further discontinuations due to AEs were observed.

4 Discussion

Based in a diverse and heterogenous population, real-life studies provide complementary information to randomized clinical trials, supporting clinical decision-making by further understanding the effectiveness of a drug in real-world conditions and a more personalized treatment approach. The REDES study included a heterogeneous population of 318 Spanish patients and a broad co-morbidity spectrum. It is striking that the percentage of allergic rhinitis is low (21%), with a percentage of the allergic population around 50%, compared to other studies that yield higher figures of up to 78% [20, 23]. The reason for the lower prevalence of rhinitis in REDES could be that, being a retrospective evaluation, mild rhinitis is often not recorded in medical records. The proportion of atopy was similar to that of MUSCA, and curiously, the proportion of nasal polyposis found in REDES was notably higher than the proportion found in the MUSCA trial [11]. The REDES study showed that mepolizumab was safe and effective in improving overall asthma control of

severe eosinophilic asthma patients by significantly reducing severe exacerbations, OCS use and blood eosinophil counts, and improving lung function and asthma control scores (ACT). Significant improvements were evident by 6 months and persisted at month 12.

The MENSA and MUSCA clinical trials demonstrated a clinically significant reduction in exacerbation rates by 53% and 58%, respectively [9, 11]. Within our sample, rates of clinically significant exacerbations were reduced during the mepolizumab treatment compared to the pre-mepolizumab period by 77.5%. The percentage reduction in exacerbations within our study was closer to what was observed within the French nATU (temporary use authorisation) early access program to mepolizumab, in which an 86.2% reduction was observed at 12 and 24 months [24]. Other studies, smaller in size, based on real-world data have reported similar reductions in exacerbations [25, 27, 29]. This is relevant, as the frequency and severity of exacerbations has been associated with a decreased health-related quality of life [30, 31]. Real-world studies have also reported improvements in OCS use, lung function and asthma control in line with our findings [26, 28, 32].

A relatively high number of patients switched from omalizumab to mepolizumab compared to other reports [33]. It should be noted that for a decade omalizumab was the only biologic on the market. This undoubtedly led to the testing of anti-immunoglobulin (Ig) E in severe patients in indications that would be questionable today.

Mepolizumab clinical trial selection requirements concerning eosinophil peripheral blood counts were set at 150 cells/μL, with efficacy below this level remaining uncertain. However, low eosinophil counts (< 150 cells/μL) are often encountered in clinical practice and are likely due to OCS use, which reduce blood eosinophils to normal or low levels, despite persistence of eosinophilic inflammation in patients with severe asthma. REDES included a prespecified stratification by blood eosinophil counts, and within our study, individuals who had counts below 150 eosinophils/μL represented 7.9% of the population, who still received substantial benefit from mepolizumab add-on treatment. Overall, while there was an observed tendency for greater improvements at higher baseline eosinophil counts, exacerbations and lung function improvements were observed irrespective of the baseline eosinophil counts. These findings are consistent with a post hoc analysis of the MENSA and DREAM studies, in which reductions in exacerbation frequency were observed for individuals with eosinophil counts ≥ 150 cells/μL and are relevant for clinical practice given current guidelines recommend mepolizumab use for patients with eosinophil counts > 150 cells/μL [8, 34].

Amongst the 98 patients who required maintenance OCS at the start of mepolizumab, 34.4% of them discontinued OCS by 6 months and 47.8% did so by 12 months. Overall,

at 12 months post-mepolizumab, the mean OCS maintenance dose was reduced by 59.9%, in line with previous studies [24, 25]. Furthermore, 53.6% of patients who were initially treated with an OCS maintenance dose ≥ 7.5 mg/day were able to reduce their OCS dose below this mark, which is relevant in terms of reducing patients' risk category and subsequent treatment to prevent glucocorticoid-induced osteoporosis according to the most recent guidelines (OSM Table 4) [33, 35]. While timewise dose reductions in clinical trials were achieved earlier, this is likely explained by a more conservative management approach and less frequent visits in real-world practice [10, 24].

In line with previous studies, we found the frequency of drug-related adverse events was low. Additionally, treatment interruptions due to adverse events only occurred in one patient after 12 months [36].

4.1 Strengths and Limitations

Overall, the REDES study illustrates the management of severe eosinophilic asthma patients by asthma specialists in a real-world setting in Spain. Treatment recommendations were likely to guide prescription practices across participating sites through the therapeutic positioning report [37]. Additionally, treatment consensus guidelines on severe asthma management are followed among specialized asthma units in Spain and regularly updated [38].

This study's main limitation is its retrospective data collection, which may be subject to missing data and time-varying confounders. To minimize this aspect, the centres participating had specialised dedicated asthma units, the majority of which had a formal accreditation by the Spanish Society of Pulmonology (SEPAR) or the Spanish Society of Allergy (SEAIC).

Finally, the lack of a control group as part of the REDES study design must be considered in interpreting the safety data since this study uses pre-treatment as a comparison (baseline).

5 Conclusions

The REDES study helps advance patient care by providing useful information to guide clinical decision-making in patients with severe eosinophilic asthma. This real-life study of severe eosinophilic asthma patients treated with mepolizumab in Hospital Asthma Units of the Spanish National Health System confirms that mepolizumab was effective in reducing clinically significant exacerbations, improving lung function and decreasing OCS dependence and mean OCS dose irrespective of baseline blood eosinophil counts. The REDES study confirms in a real-life environment the benefits of mepolizumab in severe eosinophilic asthma patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40265-021-01597-9>.

Acknowledgements We thank the REDES Study group members and collaborators who participated in the study: Mariana Muñoz Esquerre and Héctor Cabrerizo Carreño from Hospital Bellvitge, Antonio Valero, Ebymar Arismendi, Irina Bobolea and Gemma López Saiz from Hospital Clínic, Celia Pinedo Sierra from Hospital Clínic San Carlos, Francisco Javier González Barcala and Purificación Pérez López Corona from Hospital Clínic Santiago de Compostela; Jacinto Ramos González and Javier Martín Puentes from Hospital Clínic Universitario de Salamanca; Gregorio Soto Campos and Francisco Pérez Grimaldi from Hospital de Jerez; Inmaculada Lluch from Hospital de La Ribera; Juan Luis García Rivero, Celia Gutierrez Villegas and Idoia Salinas Garrido from Hospital de Laredo; Cleofé Fernández Aracil from Hospital General Universitario de Alicante; Luis Puente Maestu, Walther Iván Girón and Ángela Gómez Sacristán from Hospital General Universitario Gregorio Marañón; Miguel Díaz Palacios and Ethel Ibáñez from Hospital La Fe; Irene De Lorenzo from Hospital Nuestra Sra. De la Candelaria; Ana Sogo, Daniel Ross-Monserrate and Elena Prina from Hospital Parc Taulí; Eusebi Chiner Vives and Sandra Vañes Baños from Hospital San Juan de Alicante; Rocío Díaz Campos and Ismael García Moguel from Hospital Universitario 12 de Octubre; Carmen Montero Martínez and María Fernandez Marrube from Hospital Universitario A Coruña; Tamara Hermida Valverde and Anaís Enríquez from Hospital Universitario Central de Asturias; Nuria Marina Malanda and Ana Gómez Larrauri from Hospital Universitario de Cruces; Antonio García Dumpiérrez, Rodolfo Castillo Sainz, Nancy Ortega Rodríguez and Lourdes Almeida Quintana from Hospital Universitario Dr. Negrín; Luis Cabanes López from Hospital Universitario Dr. Peset; Santiago Quirce Gancedo, Javier Dominguez Ortega, David Romero Ribate, Irene Hernández and Daniel Laorden Escudero from Hospital Universitario La Paz; Carolina Cisneros from Hospital Universitario La Princesa; Antolín López Viña, Andrea Trisán Alonso and Teresa Caruana Careaga from Hospital Universitario Puerta de Hierro; Ana Gómez-Bastero Fernández and Lucía Marín Barrera from Hospital Virgen de la Macarena (list available in the Online Supplementary Material), Marta Rubio from IQVIA for her logistic support (in the form of contracting management, site training, database monitoring; funded by GSK) and Julieta Politi from IQVIA for her editorial support (in the form of writing assistance, development of initial draft, assembling tables and figures, collating authors' comments and referencing; funded by GSK).

Declarations

Funding This study was funded by GlaxoSmithKline (study number 213172).

Conflicts of interest CDR has received funding for travel or speaker fees from ALK, Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, Esteve, Ferrer, GSK, Menarini, Novartis, Stallergenes and Pfizer. TCD has received speaker fees from ALK, Diater, GSK, LETI and Novartis. MBA has received speaker or consulting fees from ALK, AstraZeneca, Chiesi, GSK, Novartis, Teva and Zambón. EMM has received speaker or consulting fees from ALK, AstraZeneca, BIAL, Boehringer Ingelheim, Chiesi, GSK, Novartis, Teva, and Sanofi. DBC and MGSB are employees of GSK. CDR, TCD, MBA and EMM declare no specific conflicts of interest to report regarding this paper.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and order SAS/3470/2009. Approval was granted by the Ethics Committee of Hospital La Princesa, Madrid, on 25 September 2019.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Informed consent obtained included the publication of participants' aggregate and anonymized health data.

Availability of data and material Not applicable.

Code availability Not applicable.

Author's contributions CDR, DBC, MGSB, TCD, MBA, EMM reviewed the literature and critically edited the manuscript. All authors read and approved the final version of the manuscript.


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Authors and Affiliations

Christian Domingo Ribas^{1,2}  · **Teresa Carrillo Díaz**^{3,4} · **Marina Blanco Aparicio**⁵ · **Eva Martínez Moragón**⁶ · **David Banas Conejero**⁷ · **M. Guadalupe Sánchez Herrero**⁷ on behalf of the REDES Study Group

¹ Servei de Pneumologia, Corporació Sanitària Parc Taulí, Parc Taulí s/n, Sabadell, 08208 Barcelona, Spain

² Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

³ H. Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain

⁴ Universidad de Las Palmas Gran Canaria, Las Palmas de Gran Canaria, Spain

⁵ H. Universitario A Coruña, A Coruña, Spain

⁶ H. Universitario Doctor Peset, Valencia, Spain

⁷ Specialty Care Medical Department, GlaxoSmithKline, Madrid, Spain