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Original Research Article

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Time is lung: Higher preservation of lung function in severe asthma patients after earlier mepolizumab treatment.

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Abstract

Severe asthma involves a persistent inflammation of the airways that is associated with a greater risk of exacerbations. Exacerbations are associated with a higher lung function decline over time. The prevention of lung function decline could become a strategy for disease modification, and this could be more likely to happen in patients with an earlier therapeutic approach. Thus, this study means to analyze the effect of asthma duration in clinical outcomes such as lung function, in patients from the REDES study.

REDES was an observational real-world study that assessed the effectiveness and safety of mepolizumab 100mg SC every 4 weeks for 12 months in 318 patients with severe asthma in Spain. This post hoc analysis evaluated how disease duration affected the study results through a stratification according to quartiles on their disease progression. Continuous analyses were also performed to assess the impact of confounder variables on FEV_1 (%).

At baseline, patients with shorter time of disease had a significantly higher lung function than patients with longer asthma duration. At 12 months, pre-BD FEV_1 values and the proportion of patients with ≥80% pre-BD FEV_1 were higher according to a shorter disease persistence (Q1>Q2>Q3>Q4).

These results support that time of disease persistence contributes to the lung function decline of patients with severe asthma uncontrolled while on previous treatment, and that an earlier approach with mepolizumab may imply a higher preservation of their lung function.

Keywords: severe asthma, mepolizumab, asthma duration, lung function decline, disease-modifying treatment, early approach.

Introduction

Severe Asthma (SA) is a chronic disease characterised by lung inflammation and airflow obstruction, that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires this level of treatment to prevent it from becoming uncontrolled [1, 2]. Patients with SA are generally classified into different phenotypes depending on their underlying immune dysfunction, with the IL-5-dependent pathway accounting for more than 80% of times [3]. These patients are subject to persistent type 2 (T2) airway inflammation, characterized by elevated levels of eosinophils and pro-inflammatory cytokines such as IL-5, IL-4 or IL-13 [3]. Combinations of T2 inflammation biomarkers and clinical characteristics are predictors of asthma severity, worse disease control, and future exacerbation risk [4].

Exacerbations are frequently characterized by an aggravation of the T2 inflammation that results in a compromised airflow obstruction needing systemic glucocorticoids, emergency visit or hospitalization for its management [5]. Even after the exacerbation is resolved, patients will experience long-term consequences like loss of lung function [6]. In this regard, it has been described that there is an excess of 17 mL/year loss of lung function as measured by FEV_1 in asthmatic patients who suffer exacerbations compared to patients who don't [7], but there is already a higher annual decrease of FEV_1 in asthmatic patients than in healthy controls, 38mL/year vs. 22mL/year respectively [8, 9], and this is on top of the physiological age-related lung function decline, which is described to range between 20 and 46 mL per year with a peak at 30 years, and a nadir at 62 years [10].

Altogether, it seems that T2 inflammation and exacerbations lead to an excess loss of lung function in SA patients, and although the mechanisms behind it are not fully understood, the role of IL-5 in airway epithelial cells, fibroblasts, and goblet cells is likely to contribute [11-13]. The ability of the airway tissue to repair and regenerate the self-perceived injuries, provoked by exacerbations or inflammatory effector cells (e.g. eosinophils), produces constant damage on patients' lungs, leading to structural changes in the airways, including: disruption of the epithelial barrier integrity, subepithelial fibrosis and smooth muscle hypertrophy/hyperplasia. These alterations are thought to play a major role in lung function decline and may be the cause of airway remodeling in SA patients [14, 15].

Mepolizumab is a systemic anti-IL-5 therapy approved for patients with SA and Eosinophilic Phenotype (SA-EP), Chronic Rhinosinusitis with Nasal Polyps, Eosinophilic Granulomatosis with Polyangiitis and Hypereosinophilic Syndrome [16]. The clinical effectiveness and safety of mepolizumab in SA is well established [17-23], but evidence about the effects of biologics in

airway remodeling is still limited. The aim of this post hoc analysis of the REDES study is to determine the impact of the time of disease duration on lung function in patients with mepolizumab.

Methods

REDES (GSK ID: 213172) was a retrospective, real-world, multicentric, observational cohort study enrolling patients with severe asthma across 24 Spanish hospital asthma units.

The observational period included 12 months pre- and 12 months post-mepolizumab treatment (100mg SC every 4 weeks). Eligibility criteria for the REDES study included: patients ≥18 years of age with a clinical diagnosis of severe uncontrolled asthma; patients who initiated mepolizumab ≥12 months before the date of inclusion in the study; and had ≥12 months of relevant medical records prior to enrolment. The primary endpoint was the annual rate of clinically significant exacerbations. Secondary endpoints included pre- and post-bronchodilator spirometry outcomes and other parameters related to asthma control, biomarkers, and OCS treatment.

Details of the REDES study results, design and patient population have been published previously [22]. However, the influence of disease duration in asthma clinical outcomes has not been previously reported.

Due to the retrospective nature of the REDES study and the data available, we defined the time of disease duration as the time from the age of asthma diagnosis to the age of mepolizumab initiation. Patients were then stratified in quartiles according to the time of asthma duration. Age of asthma diagnosis was included by every principal investigator from their patients' clinical records to the study eCRF (electronic Case Report Form).

Baseline features and other study assessments were analysed. Specifically, baseline features included sex, smoking status, comorbid NP, time from asthma diagnosis to mepolizumab initiation, atopic sensitization and total IgE. Study assessments included blood eosinophil counts, ACT score, annual rate of clinically significant exacerbations, prednisone dose, patients discontinuing maintenance OCS and spirometry values. Notably, a benchmark of 0.23L improvement in pre-bronchodilator FEV_1 was established, as proposed by Santanello et al., as a minimal patient perceived improvement (MPPI) [24], and the percentage of patients achieving the MPPI was calculated across the different subgroups.

Means and standard deviations (SD) were calculated for quantitative variables and percentages were used to describe proportions in dichotomous variables. Statistical significance defined as a

p value of <0.05 was calculated for the change of study assessments at 12 months in each group (intragroup), and at baseline, or 12 months between groups (intergroup). We performed Student T-tests for quantitative variables, and Chi-square tests for dichotomous variables.

To determine the relation between the time of disease progression and lung function, a continuous correlation analysis was made. To minimise other factors' influence, we performed a multivariate regression analysis, including as confounding independent variables: the time from diagnosis, age, BMI, blood eosinophil levels at baseline, exacerbations pre-treatment and exacerbations during treatment. Pre-BD FEV_1% pre and post treatment, as well as Pre-BD FEV_1% improvements were the three dependent variables assessed in three separate multivariate analysis utilizing the same confounders. Only patients with data on all independent variables and the correspondent dependent variable were included.

Three graphs were then created using bivariate models to assess the correlation between time of disease progression and: 1) pre-BD FEV1% at baseline, 2) pre-BD FEV1% after 12 months of treatment and 3) improvements in FEV1 % (Figure 3, Figure 4 and Figure 5).

These analyses were performed using the program STATISTICA v.13.5.0.63.

Results

From the total 318 patients of the REDES study, the age of asthma diagnosis had not been collected in 17, therefore, they were excluded from this analysis. 84 patients entered in Q1 (≤10 years), 74 patients in Q2 (11-20 years), 70 patients in Q3 (21-33 years), and 73 patients in Q4 (≥34 years) (Table 1).

Mean age was 53.4, 58.7, 53.5 and 61.1 years and mean time from asthma diagnosis until mepolizumab initiation was 5.7, 15.8, 26.8 and 44.6 years in Q1, Q2, Q3 and Q4, respectively. The rest of patients' baseline characteristics are shown in Table 1.

A consistent reduction in annual exacerbations was seen across all groups. Regarding asthma symptoms, ACT also improved across quartiles subgroups without an apparent influence of the time of disease persistence. OCS dose and the proportion of patients requiring maintenance OCS decreased also similarly (Table 1).

Regarding lung function, at baseline, Q1 had a statistically significant higher mean pre-BD FEV_1% predicted of 72.5% compared to 67.2% in Q3 and 66.3% in Q4, and numerically higher compared to Q2 (71.7%) (Table 2).

Figure 1 and Figure 2 illustrate that both pre-BD FEV_1% value and the proportion of patients with ≥80% pre-BD FEV_1 were higher as the disease duration was shorter (Q1>Q2>Q3>Q4), this was observed both at baseline and at 12 months (Table 2). Also, a downward trend was shown in pre-BD FEV_1% improvement after treatment: 12.30, 12.45, 9.79 and 7.39 (%), respectively. Comparable results were seen in post-BD FEV_1%, although with more variability than pre-BD (Table 2).

Looking at the proportion of patients who achieved the MPPI of 0.23L, no statistically significant differences were observed between quartiles, although it numerically decreased from Q1 to Q4 (Table 2).

Regarding the multivariate regression, at baseline, only the time of disease progression has a statistically significant negative correlation with lung function preservation measured with pre-BD FEV1 % (b*= -0.171906, p= 0.020169). While at 12 months, both the time of disease progression and the number of exacerbations during the 12-month treatment period showed statistically significant negative correlation with pre-BD FEV1 % (b*= -0.232806, p= 0.002332; b*= -0.205309, p= 0.008932, respectively).

No statistically significant associations were found when measuring the improvement in pre-BD FEV1 % pre and post treatment (b*= -0.065667, p= 0.373923).

Bivariate correlation between pre-BD FEV1%, pre and post treatment, and time of disease progression are illustrated in Figure 3 and Figure 4.

Discussion

It is well established that an early intervention in some inflammatory diseases, with proper pharmacologic agents, can halt the biological processes associated to the disease and prevent disease progression. [25]

In SA this concept is not that extended yet. However, eosinophilic functions and related damage within the airways influence the remodeling process of diseases such as severe asthma and CRSwNP [14]. Moreover, it has been reported that targeting IL-5 with mepolizumab significantly reduces the expression of airway remodelling parameters like the accumulation of tenascin, lumican and procollagen III in the bronchial mucosal reticular basement membrane [26].

In our study, patients with a prompter introduction of mepolizumab since their asthma diagnosis showed a more preserved lung function as measured by FEV_1 pre- and post-BD. Moreover, these patients achieved higher values of lung function at 12 months, compared to patients who had a later mepolizumab initiation.

Consistently with these findings, multivariate regression analyses showed an influence of the time of disease progression on the preservation of lung function at baseline, and on achieving higher values after 12 months of treatment with mepolizumab, being the latest also influenced by the patients' exacerbations during treatment.

These results support that the time of disease duration contributes to the decline of lung capacity, and that an earlier therapeutic approach with mepolizumab could imply a higher preservation of lung function. These are also aligned with previously published evidence about clinical remission, where patients that achieved clinical remission showed a less severe form of SA compared to those who did not [27]. Thus, the moment of mepolizumab initiation is crucial in achieving the best possible outcomes, as the precise targeting of T2 inflammation with mepolizumab (anti IL-5) could be able to interrupt airway remodeling.

Due to its retrospective nature, this study has several limitations. The age at which ICS treatment began wasn't documented, so it couldn't be ensured whether patients were timely treated with ICS after their asthma diagnosis. No availability of quality-of-life questionnaires was another important factor, although it has been reported that lung function improvement does not necessarily correlate with a better quality of life [28].

The relevance of lung function has not been put in question in asthma. It is, in fact, one of the main variables to define clinical remission, and several studies point out that a better-preserved lung function at baseline, increased the odds of achieving clinical remission in severe asthmatic patients, after biologic treatment [29, 30]. This reinforces the existence of an association between lung function and the course of the disease.

Apart from this, tobacco usage is a major confounding when measuring lung function, in this regard, the smoking status of the 4 groups were balanced. To note is that there were just 3 current smokers in REDES, the 3 of them included in the first quartile, and the rest being "Ex-Smokers" or "Non Smokers" in this study.

Conclusion

The results of this study suggest that the duration of disease contributes to lung function decline of severe asthma patients, uncontrolled on previous treatment, and support an earlier intervention with mepolizumab for a higher preservation of lung function.

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Conflicts of interest

FJGB has received consulting fees, payment for presentations, support for attending meetings or research grants from ALK, AstraZeneca, Bial, Chiesi, Gebro Pharma, GSK, Menarini, Novartis, Rovi, Roxall, Sanofi, Stallergenes-Greer and Teva. **IB has received speaker consulting fees from AstraZeneca, Chiesi, GSK, Novartis, Teva and Sanofi. JDO** has received funding for research, honoraria for consultancy and conferences from AstraZeneca, Chiesi and GSK; honoraria for consultancy and conferences from Bial, Novartis, Sanofi and Teva; and speaker fees from ALK, LETI Pharma and Mundipharma. **EAC** is a GSK employee. **DBC** is a GSK employee and holds GSK stocks/shares. **EMM** has received speaker or consulting fees from ALK, AstraZeneca, BIAL, Boehringer Ingelheim, Chiesi, GSK, Novartis, Teva, and Sanofi. **TCD** has received speaker fees from ALK, AstraZeneca, Diater, GSK, LETI and Novartis. **MBA** has received speaker or consulting fees from ALK, AstraZeneca, Chiesi, GSK, Novartis, Teva and Zambón. **CDR** has received funding for travel or speaker fees from ALK, Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Menarini, Novartis, Stallergenes and Pfizer.

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 the 25th of September of 2019.

Author contributions

All authors contributed to the study design. FJGB, IB, JDO, EMM, TC, MBA and CD enrolled patients. DBC and EAC performed the analyses. All authors critically reviewed and approved the manuscript.

Table 1. Baseline features and study assessments based on quartiles stratification.

Baseline features	**N**	**Q1**			**N**	**Q2**			**N**	**Q3**			**N**	**Q4**		
Sex, female, n (%)	84	57 (68)			74	51 (69)			70	50 (71)			73	52 (71)		
Comorbid nasal polyps, n (%)	84	39 (46)			74	29 (39)			70	39 (56)			73	35 (48)		
Age, mean (SD)	84	53.4 (13.8)			74	58.7 (13.5)			70	53.5 (12)			73	61.1 (8.8)		
Age of asthma diagnosis, mean (SD)	84	47.7 (14.3)			74	42.9 (13.4)			70	26.5 (3.8)			73	16.5 (9.9)		
Years from diagnosis to mepolizumab, mean (SD)	84	5.7 (2.8)			74	15.8 (3.0)			70	26.8 (3.8)			73	44.6 (7.7)		
No smokers, n/N (%)	80	46/80 (57.5)			71	51/71 (71.83)			69	46/69 (66.67)			70	47/70 (67.14)		
Atopic sensitization, n (%)	82	40 (49)			74	30 (40.5)			70	25 (35.7)			73	28 (38.4)		
Total IgE, mean (SD) IU	83	340.6 (456.4)			67	363.6 (520.8)			69	348.2 (618.5)			69	310.5 (506.1)		
Study assessments	**N**	**B**	**N**	**12M**	**N**	**B**	**N**	**12M**	**N**	**B**	**N**	**12M**	**N**	**B**	**N**	**12M**
Blood eosinophil counts, mean (SD)	84	829.88 (1051.35)	58	***113.10 (214.73)***	73	619.47 (446.96)	54	***136.33 (417.44)***	70	810.57 (1204.46)	53	***70.09 (38.33)***	73	629.19 (370.17)	51	***80.41 (84.10)***
ACT score, mean (SD)	75	12.95 (4.44)*+#	69	***21.03 (4.10)***	64	14.66 (5.52)*	59	***21.46 (3.13)***	64	14.47 (5.08)+	62	***20.48 (3.96)***	70	14.43 (5.03)#	61	***20.59 (3.95)***
Patients with ACT score ≥20, n/N (%)	75	5/75 (6.67)*	69	***55/69 (79.71)***	64	15/64 (23.44)*	59	***44/59 (74.58)***	64	10/64 (15.63)	62	***44/62 (70.97)***	70	11/70 (15.71)	61	***43/61 (70.49)***
Annual exacerbations, mean (SD)	84	4.58 (3.32)	84	***1.05 (1.44)***	74	3.97 (3.09)*	74	***0.80 (1.19)***	70	5.21 (4.18)*	70	***1.20 (1.71)***	73	4.34 (3.50)	73	***0.89 (1.20)***
Prednisone dose, mean (SD), mg/day	36	11.25 (9.07)	34	***3.31 (4.65)***	32	11.43 (9.50)	32	***4.48 (6.57)***	26	13.17 (11.31)	22	***5.11 (7.89)***	23	9.53 (7.42)	25	***3.23 (6.25)***
Patients with maintenance prednisone at baseline and 0 mg/day at 12 months, n/N (%)	28	-	28	16/28 (57.14%)	25	-	25	9/25 (36%)	16	-	16	8/16 (50%)	16	-	16	9/16 (56.25%)

B: Baseline, 12M: 12 months post treatment

*+# p<0.05 for intergroup difference at baseline

Bold + Italics: p<0.05 for the difference at 12 months vs baseline

Table 2. Spirometry values based on quartiles stratification.

Spirometry values	**Q1**				**Q2**				**Q3**				**Q4**			
	N	**B**	**N**	**12M**	**N**	**B**	**N**	**12M**	**N**	**B**	**N**	**12M**	**N**	**B**	**N**	**12M**
Pre-bronchodilator FEV_1, mean (SD), L	73	2.09 (0.78)$^{*+}$	59	***2.37 (0.72)$^{¥§}$***	61	1.85 (0.71)$^{*\#}$	51	2.04 (0.73)$^{¥¶}$	55	1.92 (0.84)^{ø}	49	***2.16 (0.86)^{b}***	55	1.61 (0.61)$^{+\#ø}$	43	1.67 (0.48)^{§¶b}
Pre-bronchodilator FEV_1, mean (SD), %	74	74.73 (24.01)$^{*+}$	59	***87.03 (20.68)$^{¥§}$***	61	71.68 (20.44)	52	***84.13 (20.87)***	56	67.24 (22.74)*	49	***77.03 (21.14)$^{¥}$***	55	66.35 (19.71)$^{+}$	43	***73.74 (21.42)§***
Patients with pre-BD FEV_1 (L) improvement >0.230L, n/N (%)	57	-	57	27/57 (47.37)	51	-	51	24/51 (47.06)	47	-	47	18/47 (38.3)	41	-	41	12/41 (29.27)
Patients with pre-BD FEV_1 ≥80%, n/N (%)	74	30/74 (40.54)	59	***40/59 (67.80)$^{¥§}$***	61	21/61 (34.43)	52	***32/52 (61.54)***	56	18/56 (32.14)	49	23/49 (46.94)$^{¥}$	55	16/55 (29.09)	43	18/43 (41.86)§
Post-bronchodilator FEV_1, mean (SD), L	54	2.24 (0.79)*	30	2.37 (0.69)$^{¥§}$	53	2.02 (0.66)$^{+}$	39	2.09 (0.53)$^{¥¶}$	48	2.04 (0.75)^{ø}	37	2.29 (0.72)^{b}	47	1.77 (0.69)$^{*+}$	42	1.83 (0.70)^{§¶b}
Post-bronchodilator FEV_1, mean (SD), %	54	80.63 (24.90)*	33	87.73 (24.29)$^{¥}$	51	79.40 (21.05)$^{+}$	40	85.57 (22.22)§	48	73.93 (22.53)	37	***85.18 (18.98)¶***	47	71.73 (23.34)$^{*+}$	44	76.93 (22.81)$^{¥§¶}$
Patients with post-BD FEV_1 ≥80%, n/N (%)	54	30/54 (55.56)	33	23/33 (69.70)	51	25/51 (49.02)	40	26/40 (65.00)	48	21/48 (43.75)	37	22/37 (59.46)	47	18/47 (38.30)	44	21/44 (47.73)
Pre-bronchodilator FVC, mean (SD), %	74	90.50 (21.03)	59	***97.36 (19.60)***	61	88.86 (21.63)	52	***97.53 (22.40)***	56	89.29 (17.68)	49	***97.70 (16.60)***	54	85.84 (17.66)	43	***93.43 (22.38)***
Post-bronchodilator FVC, mean (SD), %	53	89.13 (23.81)	32	97.59 (20.84)	50	91.34 (23.97)	38	94.74 (24.74)	48	93.14 (23.02)	38	100.89 (22.52)	47	89.44 (23.96)	44	97.74 (24.59)

B: Baseline**, 12M:** 12 months post treatment

$^{*+\#ø}$ p<0.05 for intergroup difference at baseline

$^{¥§¶b}$ p<0.05 for intergroup difference at 12 months

Bold + Italics: p<0.05 for the difference at 12 months vs baseline

References

1. Asthma, G.I.f., *Global Strategy for Asthma Management and Prevention*. 2023.
2. Plaza Moral, V., et al., *GEMA 5.3. Spanish Guideline on the Management of Asthma.* Open Respir Arch, 2023. **5**(4): p. 100277.
3. Heaney, L.G., et al., *Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort.* CHEST, 2021. **160**(3): p. 814-830.
4. Couillard, S., et al., *Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford Asthma Attack Risk Scale (ORACLE).* ERJ Open Res, 2022. **8**(1).
5. Nair, P. and P.M. O'Byrne, *Medical algorithms: Approach to adult asthma exacerbations.* Allergy, 2021. **76**(11): p. 3556-3559.
6. Busse, W.W., *Consequences of severe asthma exacerbations.* Curr Opin Allergy Clin Immunol, 2023. **23**(1): p. 44-50.
7. Bai, T.R., et al., *Severe exacerbations predict excess lung function decline in asthma.* European Respiratory Journal, 2007. **30**(3): p. 452-456.
8. Lange, P., et al., *A 15-year follow-up study of ventilatory function in adults with asthma.* N Engl J Med, 1998. **339**(17): p. 1194-200.
9. Sears, M.R., *Lung function decline in asthma.* Eur Respir J, 2007. **30**(3): p. 411-3.
10. Quanjer, P.H., et al., *Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations.* Eur Respir J, 2012. **40**(6): p. 1324-43.
11. Barretto, K.T., et al., *Human airway epithelial cells express a functional IL-5 receptor.* Allergy, 2020. **75**(8): p. 2127-2130.
12. Bajbouj, K., et al., *IL-5 receptor expression in lung fibroblasts: Potential role in airway remodeling in asthma.* Allergy, 2023. **78**(3): p. 882-885.
13. Lu, Y., et al., *Eosinophil extracellular traps drive asthma progression through neuro-immune signals.* Nat Cell Biol, 2021. **23**(10): p. 1060-1072.
14. Siddiqui, S., et al., *Eosinophils and tissue remodeling: Relevance to airway disease.* J Allergy Clin Immunol, 2023. **152**(4): p. 841-857.
15. Banno, A., et al., *Bidirectional interaction of airway epithelial remodeling and inflammation in asthma.* Clin Sci (Lond), 2020. **134**(9): p. 1063-1079.
16. European-Medicines-Agency, *EMEA/H/C/003860 - Summary of product characteristics*. 2020, Last access: May 2023.
17. Bel, E.H., et al., *Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma.* New England Journal of Medicine, 2014. **371**(13): p. 1189-1197.
18. Pavord, I.D., et al., *Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.* Lancet, 2012. **380**(9842): p. 651-9.
19. Ortega HG, L.M., Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al, *Mepolizumab treatment in patients with severe eosinophilic asthma.* N Engl J Med, 2014. **371**(13): p. 1198-207.
20. Khurana, S., et al., *Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: the COSMEX Study.* Clin Ther, 2019.
21. Pilette, C., et al., *REALITI-A Study: Real-World Oral Corticosteroid-Sparing Effect of Mepolizumab in Severe Asthma.* J Allergy Clin Immunol Pract, 2022. **10**(10): p. 2646-2656.
22. Domingo Ribas, C., et al., *REal worlD Effectiveness and Safety of Mepolizumab in a Multicentric Spanish Cohort of Asthma Patients Stratified by Eosinophils: The REDES Study.* Drugs, 2021. **81**(15): p. 1763-1774.

23. Taillé, C., et al., *Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme.* Eur Respir J, 2020. **55**(6).
24. Santanello, N.C., et al., *What are minimal important changes for asthma measures in a clinical trial?* Eur Respir J, 1999. **14**(1): p. 23-7.
25. Burgers, L.E., K. Raza, and A.H. van der Helm-van Mil, *Window of opportunity in rheumatoid arthritis - definitions and supporting evidence: from old to new perspectives.* RMD Open, 2019. **5**(1): p. e000870.
26. Flood-Page, P., et al., *Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics.* J Clin Invest, 2003. **112**(7): p. 1029-36.
27. Pavord, I., et al., *Remission outcomes in severe eosinophilic asthma with mepolizumab therapy: Analysis of the REDES study.* Front Immunol, 2023. **14**: p. 1150162.
28. Carranza Rosenzweig, J.R., et al., *The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma.* Respir Med, 2004. **98**(12): p. 1157-65.
29. Bagnasco, D., et al., *Evaluation of Clinical Remission in Best-Performing Severe Asthmatic Patients Treated for Three Years with Mepolizumab.* Biomedicines, 2024. **12**(5).
30. Carpagnano, G.E., et al., *Features of severe asthma response to anti-IL5/IL5r therapies: identikit of clinical remission.* Front Immunol, 2024. **15**: p. 1343362.

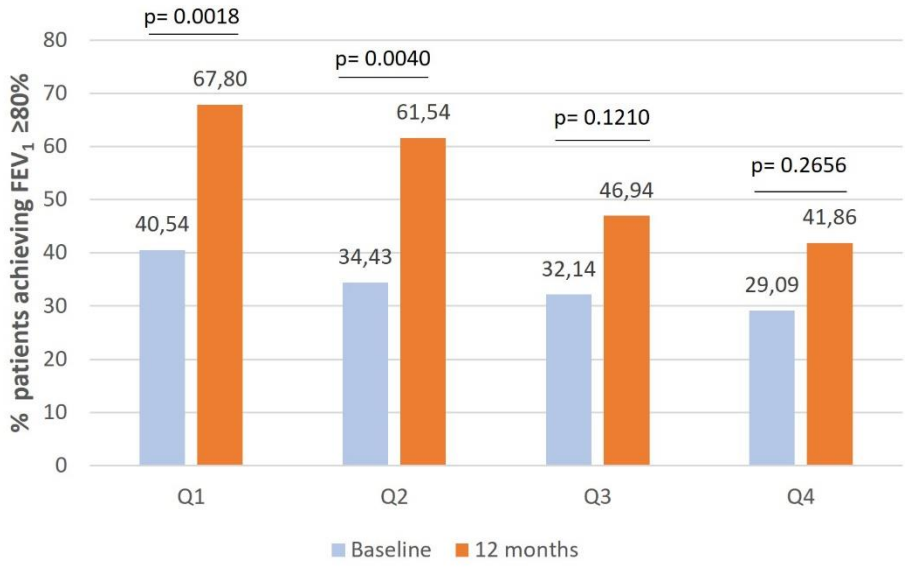

Figure 1

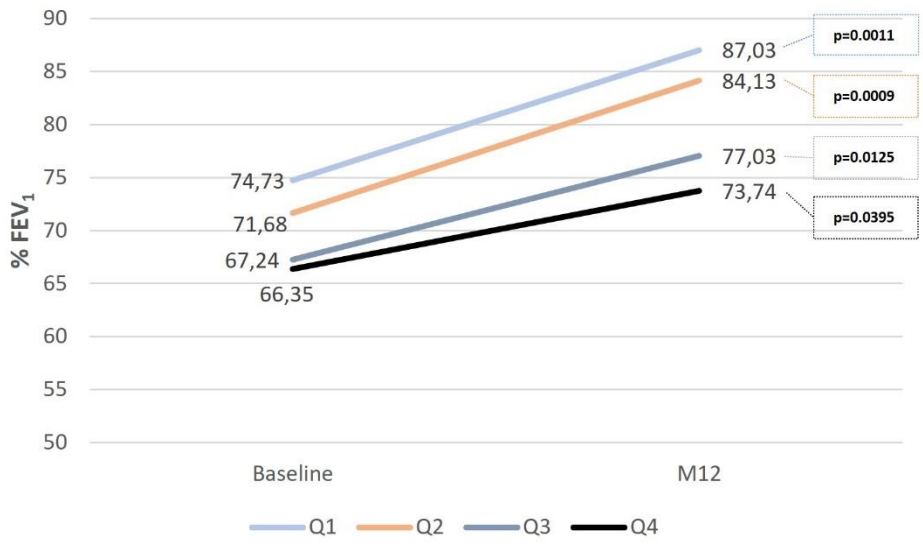

Figure 2

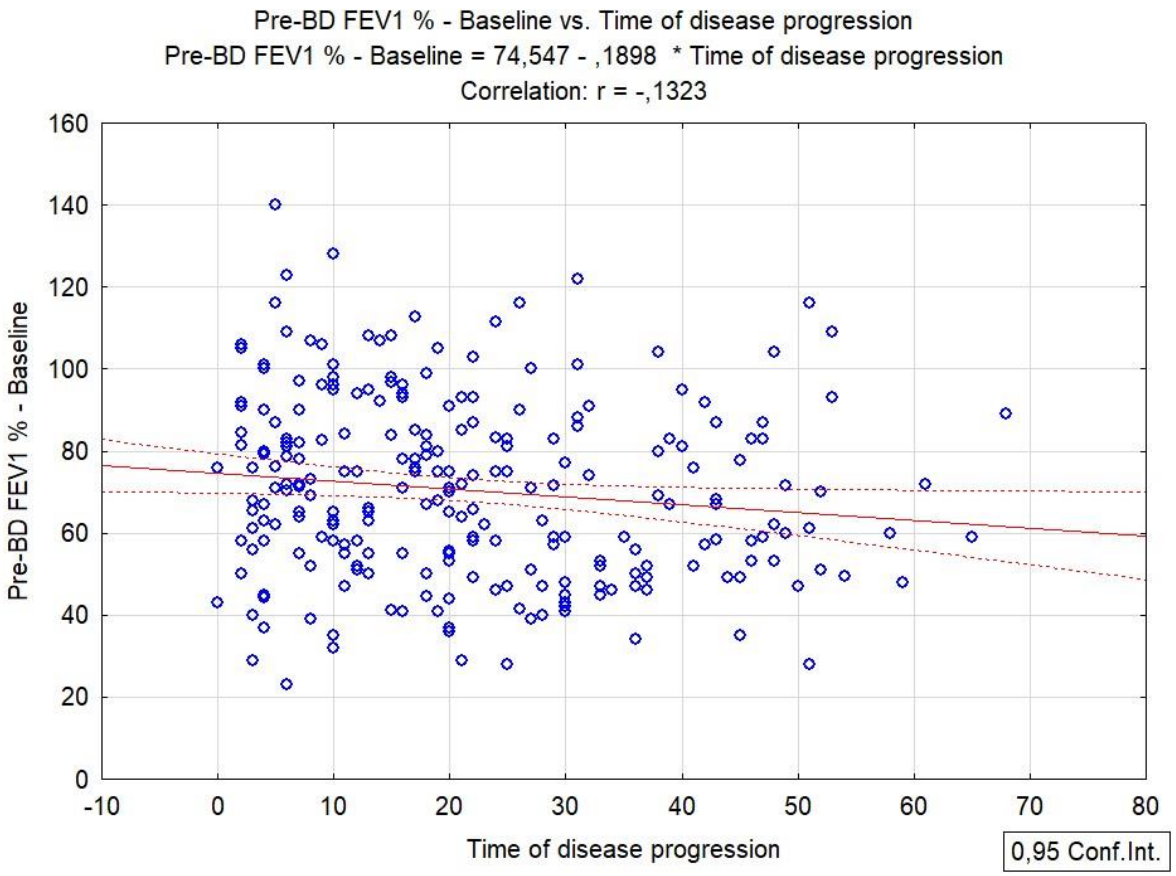

Figure 3

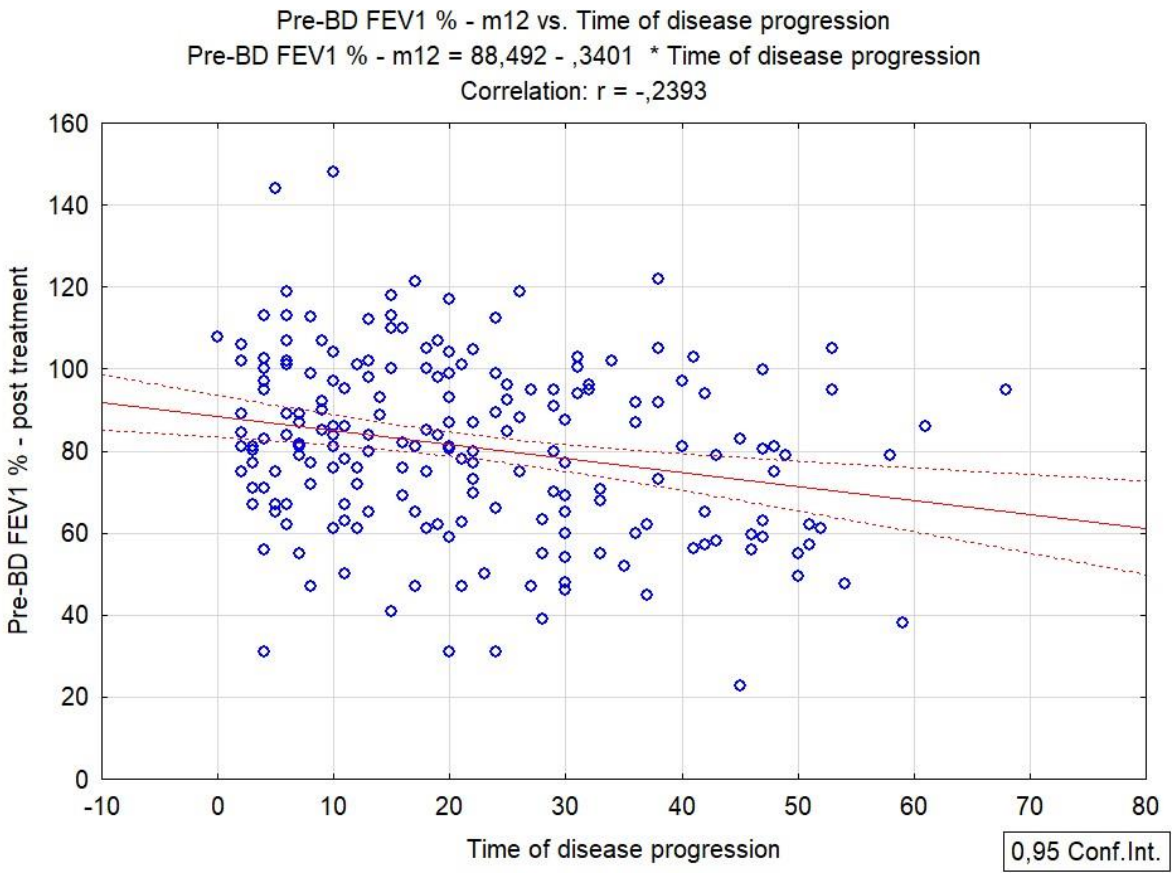

Figure 4

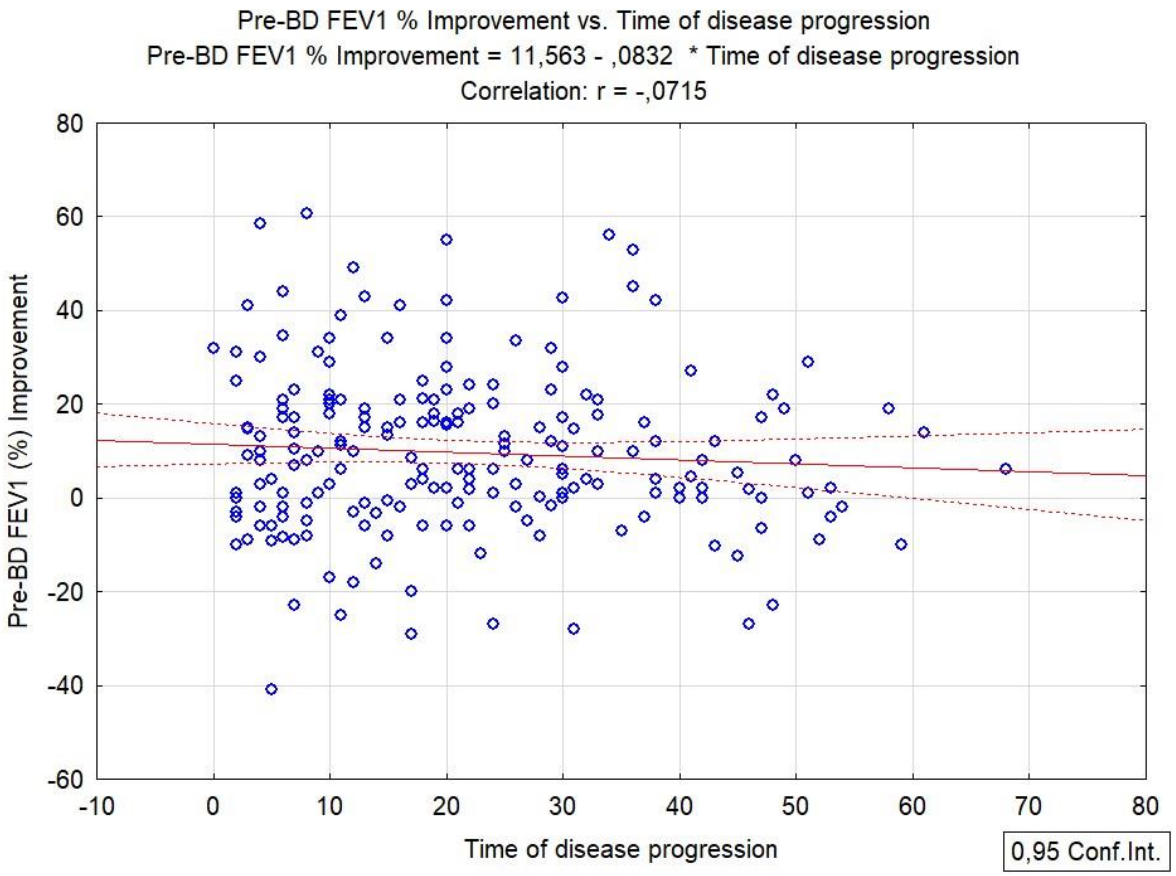

Figure 5