

## Early effectivity of dupilumab in patients with t2 severe asthma: a prospective real-life study

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Dupilumab is a fully human monoclonal antibody aimed at IL-4 receptor- $\alpha$ , inhibiting both IL-4 and IL-13 signaling [1]. Dupilumab has demonstrated efficacy in atopic dermatitis, eosinophilic esophagitis, and asthma with chronic rhinosinusitis and nasal polyposis [2-4]. Dupilumab has been shown to significantly reduce the rate of severe asthma exacerbations, improve lung function, and reduce oral corticosteroids intake in patients with uncontrolled moderate-severe asthma [5].

Previous sub-analyses of dupilumab pivotal studies have shown that lung function achieved significant improvements, both quantitatively and in terms of the rapidity of the response [6]. Other studies have revealed that dupilumab quickly suppresses nitric oxide exhaled (FeNO) and other type 2 biomarkers [7].

The publications about dupilumab in real clinical practice are limited, and most come from retrospective series [8].

We report the results of an observational, prospective, and multicentre study performed by the Registry of Severe Asthma of the Region of Murcia (RE-ASGRAMUR) under conditions of routine clinical practice in 8 reference centres in Murcia, Spain. The study was approved by a local ethics committee.

We present a series of 25 patients undergoing treatment with dupilumab for severe, uncontrolled asthma, which was confirmed by experienced pulmonologists and allergologists of one of the participating asthma units.

Our aim was to assess early response to dupilumab measuring changes in lung function (pre-bronchodilator FEV1), FeNO, asthma control (ACT) and quality of life (AQLQ). Also, other clinical characteristics, blood eosinophils and the use of oral chronic steroids (OCS) were analysed. The methods are described in [Supplementary Appendix](#).

The statistical analysis was performed using the Wilcoxon signed-rank test; the results are reported as median and interquartile range (IQR).

Our population mean age was 53.7 years and 13 were women (52%). The average BMI was 26.6; eight patients (33.3%) were current or former smokers and 15 (60%) were

atopic. Mean baseline blood eosinophils was 491.6, total IgE 698.5 and FeNO 46.3. Fifteen patients (62.5%) had nasal polyposis with a mean SNOT22 score of 62.8. Of these patients, nine (60%) had undergone an operation on at least one occasion. Nine patients (36%) received OCS at baseline, with a mean dose of 13.6 mg/d. Ten (40%) had prior treatment with another biologic agent, 5 omalizumab, 4 mepolizumab and 1 benralizumab.

In the previous year, the average exacerbation rate was 3.4, and 12 participants (52.2%) attended the emergency department at least once. The mean ACT was 13.2, AQLQ 3.6 and FEV1 2.27L (69.1%).

The demographic and clinical characteristics are detailed in [Supplementary Table 1](#).

We compare the parameters collected at baseline, four weeks and 12 weeks from the start of dupilumab. The total results are shown in [Table 1](#). [Supplementary Figure 1](#) shows the results of patients with complete data after three follow-up visits.

A significant and rapid improvement in asthma control was obtained. The median ACT score increased from 12 [10-15] to 21 [18-23] after 12 weeks of follow-up. However, at week 4, this score was already 20 (14-22) and well above the minimum clinically important difference. Also, patients with an ACT score  $\geq 20$  increased from 13% to 58% at week 4, whereas at week 12 only 2% more patients achieved that score. Rapid improvement in symptom control has also been observed in other real-life studies, although this was more progressive [9]. A longer follow-up of our series will allow us to determine whether even more relevant improvements in ACT are obtained.

Similar to other authors [6], we found a significant and rapid improvement in lung function after treatment with Dupilumab. The median FEV1 zscore increased from -2.45 [-3.2 – -1.9] to -1.64 [-2.5 – -1.2] at week 4 and to -1.37 [-1.7 – -0.5] at week 12. Furthermore, we observed that median FEV1 increased 190ml at week 4 (p 0.015) and 300ml at the end of follow-up period (p 0.008). This improvement was like that observed in phase III studies [10] and greater than that seen in other real-life studies [8].

FeNO showed a significant reduction, and we found an increase in quality of life at weeks 4 and 12 of treatment. These results confirm in real life the findings obtained during the pivotal studies of dupilumab [11].

The results of nine patients taking OCS at baseline are shown in [Supplementary Table 2](#). Six of them (67%) reduced the OCS dose by at least half during the follow-up period.

Regarding patients with polyposis, our results are like those of studies aimed at evaluating this disease [12], and details are shown in Supplementary Table 2. For patients with Atopic Dermatitis, all improved with resolution of skin lesions within the first month of dupilumab treatment.

Only one dupilumab treatment had to be withdrawn due to metrorrhagia that resolved after withdrawal of the drug. One patient presented arthralgia and another a headache at the start of treatment. Another patient had more than 1,500 blood eosinophils but had no related symptoms and the initial eosinophil count was already high. Mean eosinophils remained the same at 3 months as at baseline. However, hypereosinophilia has been described in some cases [13].

We acknowledge the limitations of our study, as it is uncontrolled, with a limited cohort size and a brief evaluation time, leading to an insufficient period to evaluate the impact on exacerbations. However, the reduction obtained in FeNO levels could be an indirect indicator of a lower risk of exacerbation [14]. Although the FEOS score is a tool designed to assess the response to treatment in patients with severe asthma from 16 weeks, and our follow-up period is shorter, we wanted to apply it to the patients in our series, obtaining an average FEOS score of 73.12 in week 12 [15].

Unlike previous real-life studies, this is a prospective study and there was a lower proportion of patients on previous steroid or monoclonal therapy [8-9]. Therefore, we believe that our sample is more representative of the population that will receive dupilumab in the future.

In conclusion, dupilumab early improved symptom control, lung function, type 2 response markers, and quality of life in our series. The response to this drug was rapid, resulting in improvements in these clinical parameters from the first twelve weeks after initiation.

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**Conflicts of Interest**

Juan Carlos Miralles López has received consultancy fees from Chiesi and speaker fees from Novartis, GSK, AstraZeneca, Sanofi, and Chiesi. Rubén Espinosa Andújar has received speaker fees from Novartis, GSK, AstraZeneca, Sanofi, and Chiesi. Manuel Castilla Martínez has received consultancy fees from GSK and AstraZeneca and speaker fees from Novartis, GSK, AstraZeneca, Sanofi, and Chiesi. Isabel María Flores Martín has received speaker fees from Novartis, GSK, Sanofi, AstraZeneca, Gebro, and Roxall. José Valverde Molina has received consultancy fees from AstraZeneca, speaker fees from Novartis, GSK, Astra Zeneca, Sanofi, Teva, Orion Pharma, and GEBRO, and fees for advisory board participation from GSK and Novartis. Miguel Enrique Reyes Cotes has received speaker fees from GSK, and AstraZeneca. Antonio Carbonell Martinez has received speaker fees from GSK, Roxal, and Immunotek. Sheila Cabrejos has received speaker fees from GSK, Novartis, Sanofi, Stallergenes, and Allergy Therapeutics. Francisco Javier Bravo Gutiérrez has received speaker fees from Novartis, Ferrer, GSK, AstraZeneca, Sanofi, and Chiesi. The remaining authors declare that they have no conflicts of interest.

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**Table 1: Results.**

Total patients (n=25)					
	Baseline (n=25)	4 weeks (n=23)	P	12 weeks (n=20)	p
ACT median [IQR]	12 [10-15]	20 [14-22]	<0,001	21 [18-23]	<0,001
AQLQ median [IQR]	3.73 [2.4-4.4]	4.40 [3.1-5.8]	<0,001	4.84 [3.7-5.9]	0,003
FEV1 L median [IQR] <sup>a</sup>	2.31 [1.6-2.6]	2.50 [1.9-3.0]	0,015	2.61 [2.1-3.4]	0,008
FEV1 ZScore median [IQR]*	-2.45 [-3.2--1.9]	-1.64 [-2.5--1.2]	0,015	-1.37 [-1.7--0.5]	0,004
FVC L median [IQR] <sup>a</sup>	3.22 [2.5-4.2]	3.27 [2.6-4.5]	0,065	3.52 [2.8-4.7]	0,015
FVC ZScore median [IQR]*	-1.54 [-2.5--1.1]	-1.17 [-2.2--0.3]	0,041	-0.77 [-2.1--0.1]	0,012
FEV1/FVC median [IQR] <sup>a</sup>	0.67 [0.58-0.72]	0.73 [0.67-0.77]	0,028	0.73 [0.72-0.76]	0,009
FEV1/FVC ZScore median [IQR]	-1.77 [-2.5--1.2]	-0.91 [-1.6--0.5]	0,034	-0.78 [-1.4--0.5]	0,009
FeNO median [IQR]	41.5 [31-53]	26 [11-33]	0,002	16 [11-29]	0,001
Eosinophils median [IQR]	400 [200-800]	NA	NA	400 [120-650]	0,24

Note: P-value of the Wilcoxon signed-rank test.

Abbreviations: IQR, interquartile range; FEV1, forced expiratory volume in 1 sec, measured before treatment; FVC, forced vital capacity, measured before treatment; L, liters; NA, not available.

<sup>a</sup> In the comparisons, only patients who had pulmonary function data at the 3 follow-up visits were considered.