Early Effectiveness of Dupilumab in Patients With Type 2 Severe Asthma: A Prospective Real-Life Study

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Dupilumab is a fully human monoclonal antibody targeting IL-4 receptor-α that inhibits both IL-4 and IL-13 signaling [1]. It has demonstrated efficacy in atopic dermatitis, eosinophilic esophagitis, and asthma with chronic rhinosinusitis and nasal polyposis [2-4]. It can significantly reduce the rate of severe asthma exacerbations, improve lung function, and reduce oral corticosteroid (OCS) intake in patients with uncontrolled moderate-severe asthma [5].

Previous subanalyses of pivotal studies on dupilumab have shown that lung function improved significantly, both quantitatively and in terms of the rapidity of the response [6]. Other studies have revealed that dupilumab quickly suppresses fractional exhaled nitric oxide (FeNO) and other type 2 biomarkers [7].

Publications on dupilumab in clinical practice are limited, and most come from retrospective series [8].

We report the results of an observational, prospective, and multicenter study performed by the Registry of Severe Asthma of the Region of Murcia (RE-ASGRAMUR) under conditions of routine clinical practice in 8 reference centers in Murcia, Spain. The study was approved by the 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 from one of the participating asthma units.

Our aim was to assess early response to dupilumab by measuring changes in lung function (prebronchodilator FEV_1), FeNO, asthma control (Asthma Control Test [ACT]), and quality of life (Asthma Quality of Life Questionnaire [AQLQ]). Other clinical characteristics, blood eosinophil count, and the long-term use of OCS were also analyzed. The methods are described in the Supplementary Appendix.

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

The mean age of the study population was 53.7 years, and 13 patients were women (52%). The average body mass index was 26.6. Eight patients (33.3%) were current or former smokers, and 15 (60%) were atopic. The mean baseline blood eosinophil count was 491.6/μL, total IgE was 698.5 kU/L, and FeNO was 46.3. Fifteen patients (62.5%) had nasal polyposis with a mean SNOT-22 score of 62.8. Of these patients, 9 (60%) had undergone at least 1 operation. Nine patients (36%) received OCS at baseline, with a mean dose of 13.6 mg/d. Ten patients (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, the mean AQLQ was 3.6, and FEV_1 was 2.27 L (69.1%).

The demographic and clinical characteristics are detailed in Supplementary Table 1.

We compare the parameters collected at baseline, 4 weeks, and 12 weeks from initiation of dupilumab. The results for the study population are shown in the Table. Supplementary Figure 1 shows the results for patients with complete data after 3 follow-up visits.

A significant and rapid improvement in asthma control was achieved. The median (IQR) 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. In addition, the percentage of patients with an ACT score ≥20 increased from 13% to 58% at week 4, whereas at week 12, only 2% more

Table. Results

	Total patients (n=25)				
	Baseline (n=25)	4 wk (n=23)	*P* Value[a]	12 wk (n=20)	*P* Value[a]
Median (IQR) ACT	12 (10-15)	20 (14-22)	<.001	21 (18-23)	<.001
Median (IQR) AQLQ	3.73 (2.4-4.4)	4.40 (3.1-5.8)	<.001	4.84 (3.7-5.9)	.003
Median (IQR) FEV_1 L[b]	2.31 (1.6-2.6)	2.50 (1.9-3.0)	.015	2.61 (2.1-3.4)	.008
Median (IQR) FEV_1 Z score[b]	–2.45 (–3.2 to –1.9)	–1.64 (–2.5 to –1.2)	.015	–1.37 (–1.7 to –0.5)	.004
Median (IQR) FVC L[b]	3.22 (2.5-4.2)	3.27 (2.6-4.5)	.065	3.52 (2.8-4.7)	.015
Median (IQR) FVC Z score[b]	–1.54 (–2.5 to –1.1)	–1.17 (–2.2 to –0.3)	.041	–0.77 (–2.1 to –0.1)	.012
Median (IQR) FEV_1/FVC[b]	0.67 (0.58-0.72)	0.73 (0.67-0.77)	.028	0.73 (0.72-0.76)	.009
Median (IQR) FEV_1/FVC Z score	–1.77 (–2.5 to –1.2)	–0.91 (–1.6 to –0.5)	.034	–0.78 (–1.4 to –0.5)	.009
Median (IQR) FeNO	41.5 (31-53)	26 (11-33)	.002	16 (11-29)	.001
Median (IQR) eosinophils	400 (200-800)	NA	NA	400 (120-650)	.24

Abbreviations: ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in 1 sec, measured before treatment; FVC, forced vital capacity, measured before treatment; IQR, interquartile range; NA, not available.
[a]Wilcoxon signed rank test.
[b]Only patients who had pulmonary function data at the 3 follow-up visits were considered for comparison.

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 enable us to determine whether even more relevant improvements in ACT are achieved.

Consistent with other authors [6], we found a significant and rapid improvement in lung function after treatment with dupilumab. The median FEV_1 Z score increased from –2.45 (–3.2 to –1.9) to –1.64 (–2.5 to –1.2) at week 4 and to –1.37 (–1.7 to –0.5) at week 12. Furthermore, we observed that median FEV_1 increased by 190 mL at week 4 (*P*=.015) and by 300 mL at the end of follow-up (*P*=.008). This improvement is similar to that reported in phase 3 studies [10] and greater than that reported in other real-life studies [8].

FeNO decreased significantly, and quality of life increased at weeks 4 and 12 of treatment. These real-world results confirm the findings reported in a pivotal trial assessing dupilumab [11].

The results of 9 patients taking OCS at baseline are shown in Supplementary Table 2. Six of these patients (67%) were able to reduce their OCS dose by at least half during the follow-up period.

Regarding patients with polyposis, our results are similar to those of studies that evaluated this disease [12] (see Supplementary Table 2). All the patients with atopic dermatitis improved, with resolution of skin lesions within the first month of dupilumab treatment.

Dupilumab had to be withdrawn in only 1 case owing to metrorrhagia, which resolved after withdrawal of the drug. One patient had arthralgia and another headache at the start of treatment. Another patient had >1500 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 reported in some cases [13].

We acknowledge the limitations of our study. It was uncontrolled, with a limited cohort size and a brief evaluation time, which was insufficient to assess the impact on exacerbations. However, the reduction in FeNO levels could be an indirect indicator of a lower risk of exacerbation [14]. Although the FEV_1, Exacerbations, Oral corticosteroids, Symptoms score is designed to assess the response to treatment in patients with severe asthma from 16 weeks and our follow-up period is shorter, we applied it in our series, obtaining an average score of 73.12 at week 12 [15].

Unlike previous real-life studies, ours was a prospective study in which a lower proportion of patients had previously received OCS or monoclonal antibody 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 led to an early improvement in 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 12 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, fees for advisory board participation from GSK and Novartis, and speaker fees from Novartis, GSK, AstraZeneca, Sanofi, Teva, Orion Pharma, and GEBRO. Miguel Henrique Reyes Cotes has received speaker fees from GSK and AstraZeneca. Antonio Carbonell Martinez has received speaker fees from GSK, Roxall, and Inmunotek. 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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