Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Real-World Response to Dupilumab as Add-on Therapy in Adults and Adolescents with Type 2 Severe Asthma: A Spanish Cohort Study

Ana Montoro Ferrer[1], María del Mar Moro Moro[2], Fernando Miguel Parra Borreguero[3], Alvaro Moreno-Ancillo[4], Alba María Extremera Ortega[5], Pedro Angel Galindo-Bonilla[5], Mar Jiménez Lara[4], José Manuel Bravo Nieto[6], Marta Jiménez Arroyo[6], José Alejandro Lemus Calderón[1], María José Espinosa de los Monteros Garde[7]

[1]Allergology Department, Hospital de Villarobledo, Albacete, Spain; [2]Allergology Department, Hospital Universitario de Toledo, Toledo, Spain; [3]Allergology Department, Hospital Virgen de Los Lirios, Alcoy, Alicante, Spain; [4]Allergology Department, Hospital de Talavera de la Reina, Toledo, Spain; [5]Allergology Department, Hospital de Ciudad Real, Ciudad Real, Spain; [6]Pneumology Department, Hospital de Talavera de la Reina, Toledo, Spain; [7]Pneumology Department, Hospital Universitario de Toledo, Toledo, Spain

Correspondence: Ana Montoro Ferrer, Allergology Department, Hospital de Villarobledo, Av. Miguel de Cervantes, Villarrobledo, Albacete, 02600, Spain, Email a.montoroferrer@gmail.com

Background: Dupilumab has demonstrated efficacy in type 2 severe asthma in clinical trials. Real-world data, particularly from Spain and including patients with prior biologic failure, remains limited. This study evaluated the effectiveness and safety of dupilumab in a Spanish cohort with type 2 severe asthma over 12 months.

Methods: Retrospective, multicenter observational study in adult and adolescent patients (≥12 years) with type 2 severe asthma treated with dupilumab for at least six months. Clinical data, including exacerbations, lung function (FEV_1), Asthma Control Test (ACT), quality of life (Mini-AQLQ), systemic corticosteroid use, and biomarkers (total IgE, eosinophil count, FeNO), were collected at baseline, 6, and 12 months. The EXACTO scale was used to assess response in non-oral corticosteroid (OCS)-dependent patients at 12 months. Subgroup analyses included chronic rhinosinusitis with nasal polyps (CRSwNP) and OCS-dependent patients at baseline.

Results: A total of 156 patients were included; 54.5% had received prior biologic therapies. Significant improvements ($p<0.005$) from baseline to 12 months were observed in exacerbations (1.43 to 0.20 per year), FEV_1 (2530.10 to 2824.59 mL), ACT (15.84 to 21.31), and Mini-AQLQ (27.24 to 74.27). Total IgE and FeNO significantly decreased whereas blood eosinophilia increased. In non-OCS-dependent patients (n=78), 56.4% were good or super-responders according to the EXACTO scale. CRSwNP patients (n=66) significantly improved in asthma and nasal symptoms. Among OCS-dependent patients (n=35), 68.6% discontinued OCS by 6 months. Comparable clinical improvements in exacerbation rates, lung function and overall response were observed in biologic-naïve and biologic-pretreated patients, consistent with similar EXACTO scores (4.92 ± 1.29 vs. 4.55 ± 1.37, respectively; $p=0.166$). No new safety signals were identified.

Conclusion: This Spanish real-world study confirms sustained effectiveness and acceptable safety of dupilumab in type 2 severe asthma, including patients with prior biologic failure and comorbid CRSwNP, supporting its use in routine clinical practice.

Plain Language Summary: Asthma is a long-term disease that makes it hard to breathe because of inflammation and narrowing of the airways. People with type 2 severe asthma often have frequent symptoms and exacerbations despite using standard treatments, and some rely on daily oral corticosteroids (OCS) to control their disease. Dupilumab is a newer medication that targets specific inflammatory pathways linked to this type of asthma. While it has proven effective in clinical studies, less is known in real-world settings, particularly in Spain.

This study reviewed the medical records of 156 adults and adolescents with type 2 severe asthma who were treated with dupilumab for at least six months at multiple centers in Spain. Researchers assessed asthma exacerbations, lung function, symptom control, quality of life, use of OCS, and blood markers over 12 months.

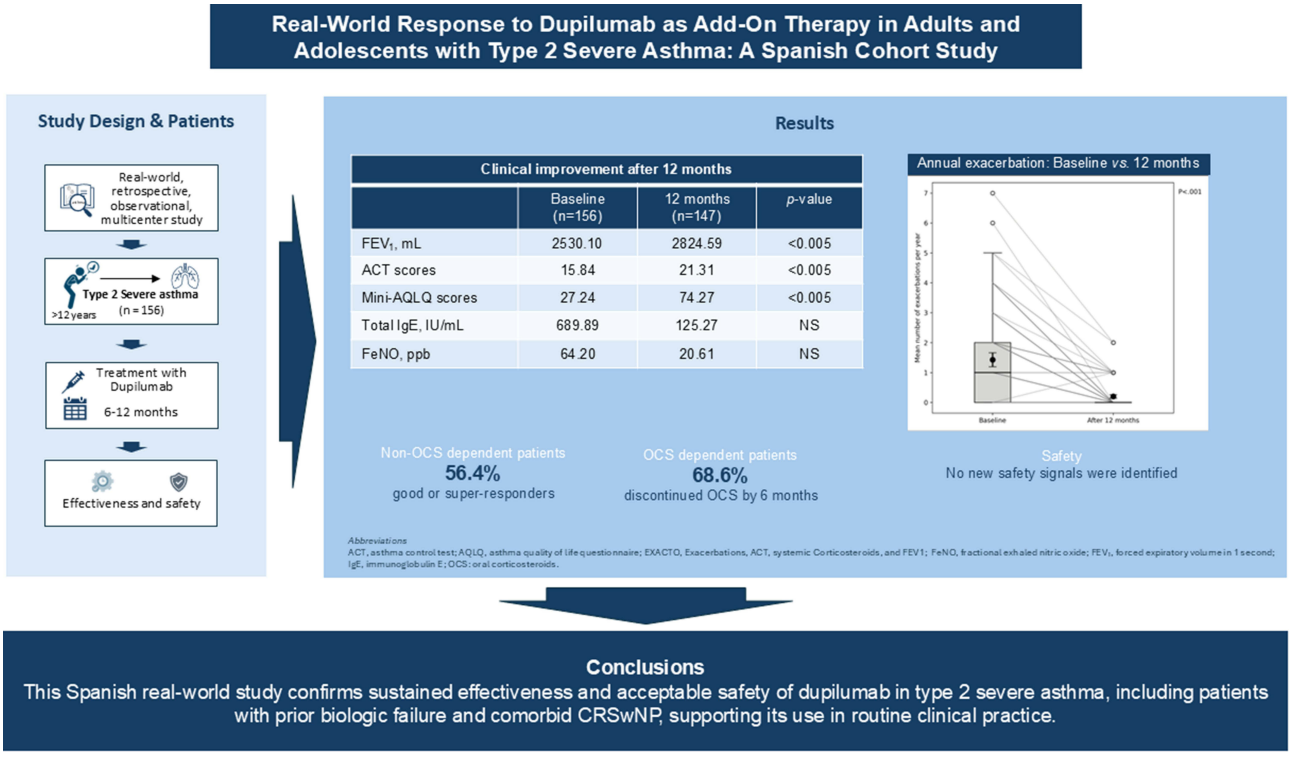
https://doi.org/10.2147/JAA.S582686
Received: 15 December 2025
Accepted: 21 February 2026
Published: 3 April 2026

After one year of treatment, patients experienced far fewer asthma exacerbations, better lung function, and improved quality of life and asthma control scores. Many patients were able to stop taking daily OCS. Those with asthma and nasal polyps also reported significant relief in their breathing and nasal symptoms. No new safety issues appeared.

These findings confirm that dupilumab works well and is safe for people with type 2 severe asthma, including those who did not respond to other biologic treatments. The results support using dupilumab in everyday clinical practice to help patients gain better control of their asthma.

Keywords: dupilumab, exacerbations, lung function, quality of life, real-world evidence, severe asthma, Spain, type 2 inflammation

Graphical Abstract



Introduction

Asthma is a common chronic respiratory disease, typified by chronic airway inflammation, airway hyperresponsiveness, and airway remodeling, affecting 1–29% of general population in different countries. Severe asthma refers to uncontrolled asthma despite adherence to maximally optimized high-dose inhaled corticosteroid – long-acting beta 2 agonist (ICS-LABA) treatment and management of contributing factors, or that worsens when high-dose treatment is decreased.[1] Thus, severe asthma is associated with frequent exacerbations and an irreversible decline in pulmonary function, affecting 5–10% of asthma patients.[2–4]

According to the pathophysiological classification, asthma can be divided into T2-High and T2-Low,[5,6] and a recent study found that the percentage of patients with severe asthma presenting T2-High inflammation was around 80%.[7] The proinflammatory cytokines IL-4, IL-5, and IL-13 have been identified as pivotal drivers of T2 inflammation in asthma and other atopic conditions.[8]

Since the introduction of the concept of "united airway disease", a large amount of epidemiological, pathophysiological, histological, and treatment-related evidence has supported the link between asthma and nasal polyps (CRSwNP).

Epidemiological studies indicate that up to 45% of patients with CRSwNP have or develop asthma. Moreover, these patients tend to have more severe asthma and experience a higher number of exacerbations.[9] In severe T2 asthma, biomarkers such as eosinophil count, IgE, and fractional exhaled nitric oxide (FeNO) are used for classification and predicting the efficacy of biological drugs.

Dupilumab is a fully humanized IgG4 monoclonal antibody targeting the α subunit of the interleukin (IL)-4 receptor, which inhibits IL-4 and IL-13 signaling. Randomized controlled trials have shown that dupilumab is effective in treating T2 asthma, reducing exacerbation rates compared to placebo.[8–11] However, there is a relative lack of real-world data, particularly within the Spanish context, and including patients who have previously shown an inadequate response to other biologic treatments. This type of evidence is crucial for confirming the translation of clinical trial results into routine clinical practice and for better understanding the response in diverse populations, including those patients with a history of suboptimal response to other biologics.

This article presents a retrospective observational analysis in patients with T2 severe asthma in Spain to assess the response after six and twelve months of treatment with dupilumab in a real-world clinical setting, especially in both naïve patients and patients who had previously received other biologic treatments without achieving adequate control of their disease, and comorbid CRSwNP, which allows us to offer valuable information on the efficacy of dupilumab in a Spanish population with severe, often refractory asthma, addressing current gaps in real-world evidence.

Materials and Methods

Study Design and Participants

This was a retrospective, descriptive, multicenter observational study involving adult patients and adolescents aged 12 years and older with type 2 severe asthma treated with dupilumab. Patients were followed in specialized severe asthma units or monographic asthma clinics within various allergy and pneumonology services in Castilla la Mancha and Alicante (Spain) for a minimum of six months. The inclusion criteria were defined by a confirmed diagnosis of asthma based on a compatible clinical history and objective evidence of variable airflow limitation, demonstrated by either a bronchodilator reversibility of ≥12% and ≥200 mL in FEV_1, a positive methacholine challenge test, or documented FEV_1 variability of ≥20%. All patients were required to be on Step 5 or 6 treatment according to the Spanish Guidelines for the Management of Asthma (GEMA 5.4), which entails maintenance therapy with high-dose inhaled corticosteroids in combination with a long-acting beta-agonist (ICS/LABA), with or without prior treatment with other biologic agents.

Patient data were collected through electronic medical records at baseline, 6 and 12 months: exacerbation rates, FEV_1 (mL), ACT scores, Mini-AQLQ scores, total IgE, blood eosinophils, and FeNO.

Due to the retrospective real-world design, follow-up duration varied across patients. All included patients had received dupilumab for at least 6 months at the time of data collection and were therefore evaluable for the 6-month analysis. Twelve-month outcomes were assessed only in patients who had reached at least 12 months of dupilumab treatment at the time of database lock. The lower number of patients with available 12-month data thus reflects differences in treatment duration rather than treatment discontinuation, loss to follow-up, or lack of response.

Procedures

Prior to initiating dupilumab, comprehensive assessments were conducted to ensure correct medication adherence and proper inhalation technique. Potential triggers and/or aggravating factors for exacerbations were identified and managed. Comorbidities such as atopic status and chronic rhinosinusitis with nasal polyps (CRSwNP) were evaluated.

Dupilumab initiation was based on the following predefined criteria, aligning with reimbursement guidelines in Spain for patients aged 12 years and older with severe asthma and type 2 inflammation: a blood eosinophil count of ≥150 cells/μL and/or a fractional exhaled nitric oxide (FeNO) level of ≥25 ppb, and a history of two or more asthma exacerbations in the previous year, or one severe exacerbation requiring hospitalization, or dependence on chronic systemic corticosteroid therapy despite optimized background asthma treatment.

Patients who received dupilumab for a minimum of six months were included in the study, regardless of whether they were biologic-naïve or had prior exposure to other biologic therapies.

Study Endpoints and Objectives

The primary objectives of this study were to: (1) Evaluate treatment response in non–oral corticosteroid–dependent patients at 12 months using the EXACTO (Exacerbations, ACT, systemic Corticosteroids, and FEV_1) scale (partial responders [EXACTO 2–4], good responders [EXACTO 5–6], and super-responders [EXACTO 7], with super-responders defined as those achieving improvement across all evaluated domains). The EXACTO scale integrates clinically relevant domains reflecting disease control and treatment response.[12] (2) Assess clinical response at 6 and 12 months of treatment; and (3) Analyze changes in biochemical and analytical parameters (total IgE, eosinophil count, FeNO). Secondary objectives included: (4) Conducting subgroup and sensitivity analyses for patients with CRSwNP, OCS-dependent patients and biologic naïve patients; and (5) Appraising the safety profile of dupilumab during the follow-up period.

Statistical Analysis

Qualitative variables are presented as frequencies and percentages, while quantitative variables are presented as means with standard deviations (SD). Paired sample t-tests were used to evaluate changes in clinical and biochemical parameters from baseline to 6 and 12 months.

Univariate analyses, including Student's t-tests for continuous variables and chi-square tests for categorical variables, were performed to compare baseline characteristics and clinical outcomes between subgroups, such as CRSwNP vs. non-CRSwNP, biologic-naïve vs. pretreated, OCS-dependent vs. non-dependent, and groups defined by comorbidities (allergic rhinitis, CRSwNP, EREA, and atopic dermatitis), baseline FeNO levels (>40 ppb vs. ≤40 ppb), Eos levels (≥150 cells/μL, ≥300 cells/μL and ≥500 cells/μL) and baseline FEV_1 above or below the cohort mean. For the EXACTO scale, each of the four domains (exacerbations, ACT, systemic corticosteroid use, and FEV_1) was scored from 0 to 2 points, resulting in a total score ranging from 0 to 7. Patients were classified as partial responders (EXACTO scores 2–4), good responders (score 5–6), or super-responders (score 7). A complete response was defined as an EXACTO score of 7. Comparisons between partial responders and good/super-responders were performed to explore baseline characteristics and clinical outcomes associated with treatment response.

A complete-case approach was used for statistical analyses, and no imputation of missing data was performed. Subgroup analyses were considered exploratory. No formal adjustment for multiple comparisons was applied; therefore, results from subgroup analyses should be interpreted cautiously. Statistical significance was set at a p-value <0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows Version 23.0. The analysis and reporting followed recommended statistical standards for observational real-world studies.[13]

Results

Participants' Characteristics

A total of 156 patients were enrolled in the study. After six months of treatment, data was analyzable for 147 patients, and at 12 months, for 106 patients. The reason for missing data at 12 months was primarily due to incomplete electronic medical records at the time of data extraction.

Demographic and clinical characteristics of the 156 patients at baseline are presented in Table 1. Briefly, the study population had a mean age of 45.58 years, with a predominance of females (62.6%), and 10 patients were adolescents. Based on T2 biomarkers, 26.5% had an eosinophilic phenotype (Eos >300 cells/μL and IgE <100 IU/mL), 24.5% allergic (Eos <300 cells/μL and IgE >100 IU/mL), and 49.0% allergic-eosinophilic (Eos >300 cells/μL and IgE >100 IU/mL). At baseline, 22.6% were dependent on oral corticosteroids, and 54.5% had received prior biologic treatment. The mean ACT score was 15.84, indicating poorly controlled asthma in the majority (76.4%) of patients. Common comorbidities included allergic rhinitis (66%), CRSwNP (42.3%), and GERD (26.9%). The mean baseline FEV_1 was 2530.10 mL, with an average of 1.43 exacerbations and 1.93 courses of systemic corticosteroids in the preceding year. Mean baseline biomarker levels were total IgE 633.4 IU/mL, eosinophils 369.2 cells/μL, and FeNO 62.64 ppb. Of the 85 patients on previous biologics, the primary reasons for switching to dupilumab were lack of asthma response in 47 (55.3%) and lack of CRSwNP response in 18 (21.2%).

Table 1 Demographic and Clinical Characteristics at Baseline

Parameters	All Patients (n = 156)
Gender	
Male	58 (37.4%)
Female	97 (62.6%)
Age, years	45.58 (16.22)
BMI	27.61 (6.64)
T2 endotype	
Eosinophilic	41 (26.5%)
Allergic	38 (24.5%)
Allergic-eosinophilic	76 (49.0%)
Corticosteroid dependence	
No	120 (77.4%)
Yes	35 (22.6%)
Naïve to biologic	
No	85 (54.5%)
Yes	71 (45.5%)
More than 2 previous biologics	29 (34.5%)
ACT	
≥ 20	35 (23.6%)
< 20	113 (76.4%)
Comorbidities	
Allergic Rhinitis	102 (66%)
CRSwPN	66 (42.3%)
GERD	42 (26.9%)
Food allergy	35 (22.4%)
N-ERD	32 (22.1%)
Atopic Dermatitis	31 (19.9%)

Notes: Values are shown as mean (SD) or n (%).
Abbreviations: ACT, asthma control test; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; GERD, gastroesophageal reflux disease; N-ERD, nonsteroidal anti-inflammatory drug exacerbated respiratory disease.

Clinical Response to Dupilumab According to the EXACTO Scale in Non-Oral Corticosteroid-Dependent Patients

The distribution of EXACTO scores at 12 months in the 78 non-oral corticosteroid-dependent patients with available data is shown in Table 2. A substantial proportion, 44 patients (56.4%), were classified as good or super-responders (EXACTO ≥5), with 7 (9.0%) achieving a complete response (EXACTO = 7).

https://doi.org/10.2147/JAA.S582686

Table 2 Non-Corticoid Dependent Patients According to EXACTO Scale After 1 year of Dupilumab Treatment

EXACTO	All Patients (n = 78)
2.00	2 (2.6%)
3.00	8 (10.3%)
4.00	24 (30.8%)
5.00	16 (20.5%)
6.00	21 (26.9%)
7.00	7 (9.0%)
Total	78 (100.0%)

Notes: Values are shown as n (%). EXACTO scale: 0–1, non-responder; 2–4, partial responder; 5–6, good responder; 7, super-responder.
Abbreviations: EXACTO, Exacerbations, ACT, systemic Corticosteroids, and FEV_1.

Comparisons were also conducted between partial responders (EXACTO scores 2–4) and good/super responders (EXACTO scores 5–7) to explore differences in baseline characteristics to identify possible super responders, but no relevant differences were found among subgroups.

Good/super responders were slightly younger than others (mean 41.9 vs. 45.9 years), but this was not statistically significant. Sex distribution and disease duration were also similar between groups. Among T2 biomarkers, only baseline blood eosinophil counts were significantly higher in good/super responders (460 vs. 312 cells/μL; p=0.036), indicating a potential predictive role as a response biomarker for dupilumab. Other biomarkers—historical eosinophils, FeNO, and IgE—were also numerically higher in this group, though differences did not reach significance.

Clinical Improvement and Changes in Biochemical and Analytical Parameters After 6 and 12 Months of Dupilumab Treatment

Table 3 summarizes the changes in key clinical and biochemical parameters from baseline to 6 and 12 months of dupilumab treatment. Statistically significant improvements were observed in the mean number of exacerbations (baseline 1.43 vs. 0.12 at 6 months and 0.20 at 12 months; p<0.005 for both) (see Figure 1), systemic corticosteroid courses (baseline 1.93 vs. 0.29 at 6 and 12 months; p<0.005 for both), FEV_1 in mL (baseline 2530.10 mL vs. 2719.09 mL at 6 months and 2824.59 mL at 12 months; p<0.005 for both), and percent predicted FEV_1 (baseline 77.45% vs. 90.89% at 6 months and 90.80% at 12 months; p<0.005 for both). ACT scores and Mini-AQLQ scores showed significant increases, indicating improved asthma control and quality of life (p<0.005 for all). Significant reductions were also seen in total IgE and FeNO levels at both 6 and 12 months (p<0.005 for all). Eosinophil counts showed a statistically significant increase at 6 months compared to baseline (367.02 vs. 566.67 cells/μL; p<0.005) and this increase was sustained at 12 months (561.77 cells/μL; p=NS vs. 6 months).

We performed a subgroup analysis to assess the efficacy of dupilumab in reducing exacerbations and improving lung function based on several cut-off points for baseline blood eosinophil counts, FeNO, and median baseline FEV_1. For eosinophils, three thresholds were used (150, 300, and 500 cells/μL), and subgroups were evaluated above and below each cut-off. Although differences were observed, they were not statistically significant, and no consistent trend was identified across groups. For FeNO, a cut-off of 40 ppb was applied; patients with FeNO > 40 ppb showed a greater reduction in exacerbations, as expected, but this was not statistically significant. Finally, the median baseline FEV_1

Table 3 Clinical Improvement and Changes in T2 Biomarkers After 6 and 12 months of Dupilumab Treatment

	Baseline (n=156)	After 6 Months (n=147)	After 12 Months (n=106)
Exacerbations	1.43 (1.44)	0.12 (0.36)*	0.20 (0.63)*
FEV_1, mL	2530.10 (866.77)	2719.09 (920.10)*	2824.59 (869.03)*
FEV_1, %	77.45 (21.15)	90.89 (18.62)*	90.80 (19.49)*
No. of courses of steroids	1.93 (2.40)	0.29 (0.67)*	0.29 (0.85)*
Total IgE, IU/mL	689.89 (979.07)	283.12 (436.06)*	125.27 (185.96)*
Eos, cells/μL	367.02 (376.80)	566.67 (578.80)*	561.77 (765.99)
FeNO, ppb	64.20 (49.08)	19.70 (14.23)*	20.61 (12.81)*
ACT	15.84 (7.33)	20.83 (4.77)*	21.31 (4.85)*
Mini-AQLQ	27.24 (30.89)	78.70 (24.19)*	74.27 (28.07)*

Notes: Values are shown as mean (SD). * Significant difference vs. baseline ($p<0.005$). Exacerbations and systemic corticosteroid courses represent events occurring during each evaluation interval (12 months pre-baseline, 0–6 months, and 0–12 months of treatment).

Abbreviations: ACT, asthma control test; AQLQ, asthma quality of life questionnaire; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; No., number; ppb, parts per billion.

(2530.1 mL) was used as a threshold. Those with more severe obstruction at baseline ($FEV_1 \leq 2530.1$ mL) demonstrated a greater improvement in lung function (baseline 2045.48 mL vs. 2172.68 mL at 12 months) compared with patients with higher initial FEV_1 (baseline 3444.05 mL vs. 3395.53 mL at 12 months).

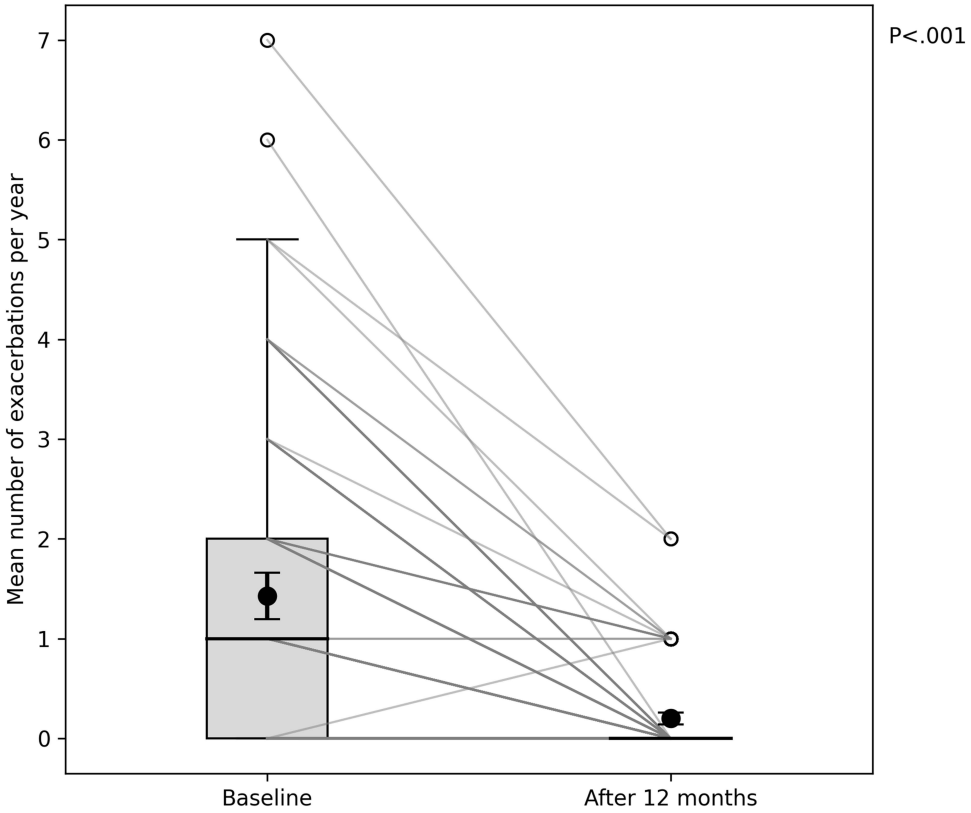


Figure 1 Annual exacerbation rate reduction: Baseline vs. 12 months.

https://doi.org/10.2147/JAA.S582686

Subgroup Analysis in Patients with CRSwNP

Table 4 presents the baseline characteristics of the 66 patients with comorbid asthma and CRSwNP. Table 5 shows the clinical improvements in this subgroup. Significant improvements were observed at 12 months in asthma exacerbations,

Table 4 Demographic and Clinical Characteristics at Baseline of CRSwNP Patients

Parameters	**CRSwNP Patients (n = 66)**
Age, years	52.35 (12.04)
BMI	27.63 (7.00)
More than 2 previous biologics	14 (40.0%)
ACT	
≥ 20	20 (32.8%)
<20	41 (67.2%)
Pulmonary function, exacerbations and corticosteroid treatment	
FEV_1, mL	2491.36 (887.74)
Exacerbations	1.08 (1.29)
No. of courses of steroids	1.42 (1.36)

Notes: Values are shown as mean (SD) or n (%).
Abbreviations: ACT, asthma control test; BMI, body mass index; FEV_1, forced expiratory volume in 1 second.

Table 5 Clinical Improvement and Changes in T2 Biomarkers After 6 and 12 months of Dupilumab Treatment in CRSwNP Patients

	Baseline (n=66)	**After 6 Months (n=60)**	**After 12 Months (n=42)**
Exacerbations	1.08 (1.29)	0.05 (0.22)*	0.10 (0.37)*
FEV_1, mL	2491.36 (887.74)	–	2728.45 (905.48)*
FEV_1, %	83.23 (21.42)	–	95.91 (19.50)*
No. of courses of steroids	1.42 (1.36)	0.15 (0.36)*	0.14 (0.42)*
Total IgE, IU/mL	413.37 (477.42)	142.53 (262.58)*	85.00 (131.06)*
Eos, cells/μL	451.05 (409.10)	817.59 (698.02)*	723.50 (647.73)
FeNO, ppb	73.36 (58.72)	22.22 (13.60)*	21.38 (15.17)*
ACT	17.66 (9.51)	22.12 (3.59)*	22.58 (3.93)*
SNOT22	54.96 (20.16)	21.00 (19.67)*	15.06 (12.39)*
VAS smell	8.62 (2.60)	2.79 (2.33)*	3.13 (1.92)*
VAS obstruction	7.36 (2.69)	1.42 (1.42)*	1.92 (1.38)*

Notes: Values are shown as mean (SD). * Significant difference vs. baseline ($p<0.005$). Exacerbations and systemic corticosteroid courses represent events occurring during each evaluation interval (12 months pre-baseline, 0–6 months, and 0–12 months of treatment).
Abbreviations: ACT, asthma control test; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; No., number; ppb, parts per billion; SNOT22, sino-nasal outcome test 22; VAS, visual analogue scale.

https://doi.org/10.2147/JAA.S582686

systemic corticosteroid courses, total IgE, FeNO, FEV_1, ACT scores, and also in CRSwNP-related outcomes such as SNOT-22, VAS smell, and VAS obstruction ($p<0.005$ for all).

Regarding the sensitivity analyses in patients with CRSwNP versus patients without CRSwNP, at baseline, patients with CRSwNP had numerically higher FeNO levels (73.36 vs. 55.98 ppb, $p=0.06$) but no significant differences in other baseline characteristics. At 12 months, both groups showed significant improvements in asthma outcomes, with no statistically significant differences between subgroups in the magnitude of improvement in exacerbation rates (CRSwNP: −0.98 vs. non-CRSwNP: −1.29, p=NS) or FEV_1 (CRSwNP: +237.09 mL vs. non-CRSwNP: +311.87 mL, p=NS).

Subgroup Analysis in Oral Corticosteroid-Dependent Patients

Of the 35 patients dependent on oral corticosteroids at baseline, 24 (68.6%) were no longer dependent at 6 months. The mean number of corticosteroid courses significantly decreased in this group from baseline to 6 months (1.93 to 0.29; $p<0.005$). The comorbidity of atopic dermatitis was significantly associated with persistent corticosteroid dependence at 6 months ($p=0.035$). No significant association was found between T2 endotype and corticosteroid dependence at 6 months.

Regarding the sensitivity analyses in OCS-dependent versus non-OCS-dependent patients, as expected, OCS-dependent patients had a higher number of baseline exacerbations and lower baseline FEV_1. The proportion of patients achieving asthma control (ACT ≥20) at 12 months was numerically lower in the OCS-dependent group, but this did not reach statistical significance ($p=0.08$).

Subgroup Bio-Naïve

A total of 85 patients (54.5%) were previously treated with biologics approved for severe asthma mainly omalizumab and anti–IL-5 agents (mepolizumab, benralizumab, or reslizumab). The primary reasons for switching to dupilumab were lack of asthma control and/or insufficient response of comorbid CRSwNP. Noteworthy, most switches from omalizumab to dupilumab were driven by inadequate asthma control, while patients who had received more than two biologics were switched to dupilumab due to insufficient control of both asthma and CRSwNP.

Biologic-pretreated patients had a longer duration of asthma (mean 18.2 vs. 12.5 years, $p<0.01$) in comparison with biologic-naïve patients. Both groups showed significant improvements in exacerbation rates and FEV_1 at 12 months, with no statistically significant differences between subgroups in the extent of these improvements.

Improvements in asthma control were also observed in both groups, as reflected by significant increases in ACT scores over time. Overall response according to the EXACTO scale was comparable between biologic-naïve and biologic-pretreated patients (mean EXACTO total 4.92 ± 1.29 vs. 4.55 ± 1.37, respectively; $p=0.166$), supporting a consistent multidimensional clinical benefit of dupilumab regardless of prior biologic exposure.

Safety Analysis and Discontinuation of Treatment

Safety data were obtained from routine clinical records, including reported adverse events, treatment discontinuations, and physician free-text observations. Dupilumab was generally well tolerated in this real-world cohort. Reported adverse events were infrequent and mostly mild. The most recorded events included injection-site reactions and transient increases in blood eosinophil counts.

Conjunctivitis, a known adverse event associated with dupilumab, was rarely reported and did not lead to treatment discontinuation in any case. This low incidence is consistent with prior studies showing that conjunctivitis occurs less frequently in asthma patients than in those with atopic dermatitis. It has been hypothesized that the latter group may have pre-existing ocular surface alterations—such as epithelial barrier dysfunction or microbiome imbalance—that predispose them to IL-4/IL-13–mediated inflammation. In contrast, asthma patients typically lack these baseline ocular abnormalities, which could explain the lower susceptibility.

No cases of severe hypersensitivity or unexpected adverse events were detected, and treatment discontinuation was mainly due to perceived lack of efficacy rather than safety concerns. Overall, no new safety signals beyond those previously described in clinical trials and real-world studies were observed.

Discussion

This retrospective, multicenter observational study assessed the real-world response to dupilumab in adult and adolescent patients with type 2 severe asthma over a 12-month period. The findings largely corroborate the efficacy of dupilumab observed in pivotal clinical trials[14–16] and other real-world evidence studies,[17–20] demonstrating a significant reduction in asthma exacerbations, improvement in lung function, and enhanced quality of life after both six and twelve months of treatment in this patient population. Importantly, these benefits were observed in a challenging population, including patients with prior biologic failure and comorbid CRSwNP.

A particularly relevant finding of this real-world study is the consistent clinical benefit of dupilumab observed in patients previously treated with other biologic therapies, who represented more than half of our cohort. These biologic-pretreated patients, mainly exposed to omalizumab and anti–IL-5 agents due to inadequate control of asthma and/or comorbid CRSwNP, had a significantly longer duration of disease, suggesting a more complex and treatment-refractory population. Despite this, dupilumab led to meaningful improvements in exacerbation rates, lung function, and asthma control at 12 months, with a multidimensional treatment response comparable to that observed in biologic-naïve patients, as reflected by similar EXACTO scores. These findings support the effectiveness of dupilumab even after failure of previous biologic therapies and reinforce its role as a valuable therapeutic option in difficult-to-treat type 2 severe asthma in routine clinical practice.

The baseline characteristics of our cohort reflect a typical profile of patients with poorly controlled severe asthma,[4] often with a high burden of T2-associated comorbidities such as allergic rhinitis and nasal polyposis, and elevated type 2 inflammatory biomarkers, aligning with the expected phenotype of dupilumab responders.[7,8]

The application of the EXACTO scale in our non-OCS-dependent subgroup revealed that over half of the patients achieved a good or complete response at 12 months, providing a structured assessment of multi-domain clinical improvement in a real-world setting. To our knowledge, this is the first study to incorporate EXACTO as an outcome measure for evaluating the efficacy of dupilumab in a cohort exceeding 100 patients, underscoring the clinical relevance of dupilumab beyond single-domain outcomes like exacerbations reduction or pulmonary function. Furthermore, our findings demonstrate that patients with elevated type 2 inflammatory biomarkers (eosinophils, FeNO and/or IgE) are more likely to achieve a good or complete response to dupilumab, thereby reinforcing their predictive value within a multidimensional clinical framework and supporting observations previously reported in randomized clinical trials. However, among these biomarkers, only blood eosinophil counts showed a statistically significant association with treatment response, probably due to a limited sample size.

The substantial 90% reduction in exacerbation rates from baseline observed in our study is particularly noteworthy, especially considering that a significant proportion of our cohort (54.5%) had previously failed other biologic therapies, representing a potentially more treatment-resistant population. This reduction exceeds that reported in some other real-world studies,[20] highlighting the potential benefit of dupilumab even in those with prior biologic exposure. Improvements in ACT and Mini-AQLQ scores paralleled these findings, highlighting the impact of dupilumab on both symptom control and patient-reported outcomes, consistent with previous reports.[17] Besides, the sustained improvement in FEV_1, with an average increase of over 290 mL at 12 months, further underscores dupilumab's ability to improve airflow limitation in this severe asthma population, aligning with findings from other real-world studies in Spain and internationally.[18,19]

FEV_1 was analyzed using absolute values (mL) to assess intraindividual longitudinal changes over time. Given the substantial proportion of women and adolescents in our cohort, comparisons based on absolute FEV_1 values between subgroups should be interpreted with caution, as lung function is influenced by age, sex, and height. Accordingly, we avoided overinterpretation of between-group differences based solely on absolute FEV_1 values.

Regarding biomarkers, both FeNO and total IgE levels declined significantly over the course of treatment. Subgroup analyses of these biomarkers provide additional insights. Although differences across eosinophil and FeNO cut-offs were not statistically significant, patients with more severe baseline airflow obstruction appeared to experience greater gains in lung function. This observation, while exploratory, raises the possibility that dupilumab could influence airway remodeling—a concept that merits investigation in long-term, mechanistic studies. The recent VESTIGE clinical trial[21] showed that dupilumab reduced mucus plug scores and improved lung function in patients with moderate-to-severe asthma with

high baseline mucus plug score, proving an important effect in airway remodeling. Similarly, the consistent benefit observed in patients with CRSwNP reinforces the role of dupilumab in managing united airway disease, with improvements documented in both asthma and sinonasal outcomes, as evidenced by reductions in SNOT-22 and VAS scores, alongside improvements in exacerbation rates and lung function. Interestingly, our preliminary subgroup comparisons did not reveal significant differences in the magnitude of asthma improvement between patients with and without CRSwNP, suggesting a consistent effect of dupilumab on asthma outcomes regardless of comorbidities. These findings support the growing evidence for the role of dupilumab in patients with comorbid type 2 inflammatory conditions.[22,23]

The observed increase in eosinophil counts is a well-documented phenomenon after dupilumab initiation, particularly evident at 6 months. While dupilumab primarily targets IL-4 and IL-13 signaling—cytokines involved in the regulation of eosinophil trafficking—its mechanism does not directly affect IL-5–driven eosinophilopoiesis. IL-4/IL-13 signaling plays a key role in regulating eosinophil tissue migration via modulation of vascular cell adhesion molecule 1 (VCAM1) expression in endothelial cells. Inhibiting this pathway may reduce eosinophil migration into tissues while allowing continued bone marrow egress regulated by IL-5, resulting in elevated peripheral eosinophil counts. However, it has been reported that this transient increase in eosinophil counts with dupilumab treatment did not affect efficacy and were rarely of clinical consequence.[24] Eosinophilia (>3000 cells/μL) was observed in some patients; however, none developed clinical manifestations compatible with hypereosinophilic syndromes or eosinophilic granulomatosis with polyangiitis (EGPA).

In line with the VENTURE trial,[15] our study demonstrated a substantial reduction in oral corticosteroid (OCS) dependence, with nearly 70% of previously dependent patients discontinuing OCS by six months. Observational data similarly report a decline in chronic OCS use from ~40% to 15% at one year.[20] These findings reinforce the corticosteroid-sparing effect of dupilumab in real-world settings and underscore its potential to reduce the burden of steroid-related adverse effects.

Dupilumab showed similar efficacy in biologic-naïve and previously treated patients, reinforcing its value even after failure of anti–IL-5 or anti-IgE therapies. Recent European findings suggest that dual IL-4/IL-13 blockade may confer additional benefits in selected cases.[25]

The discontinuation rate in our study (14.1%), with a small proportion due to adverse events, suggests a favorable real-world safety profile for dupilumab, consistent with clinical trial data.[14]

We acknowledge some limitations inherent to our study design. The retrospective and observational nature introduces potential biases such as selection and reporting biases and missing data. The EXACTO score analysis was indeed limited to a subset of patients, due to some missing data on OCS dose in OCS-dependent patients, and the descriptive nature of our subgroup analyses could limit the strength of our conclusions regarding differential treatment effects across subgroups. Furthermore, the lack of a placebo control group limits our ability to definitively attribute the observed improvements solely to dupilumab.

Future research should focus on prospective studies with larger sample sizes and control groups to validate these real-world findings. Longitudinal analyses of biomarker changes in relation to clinical response, as well as detailed characterization of non-responders, are crucial to further optimize patient selection and treatment strategies. Multivariate analyses to adjust for potential confounders and formal interaction testing in subgroup analyses are also warranted.

Conclusion

In conclusion, this multicentric, retrospective study from Spain provides further evidence for the effectiveness and safety of dupilumab in treating adults and adolescents with type 2 severe asthma over a 12-month period in real-world clinical practice. Dupilumab appears to be an effective and safe biological therapy for patients with severe asthma, regardless of prior biologic treatment failure or the presence of comorbid CRSwNP.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article. Any other information related to this study is available from the corresponding author, upon reasonable request.

Ethical Approval and Informed Consent

The Registry adheres to the fundamental ethical principles of nonmaleficence, justice, autonomy, and beneficence, as well as the ethical norms set forth in the Declaration of Helsinki (1964, and subsequent amendments). Furthermore, the registry maintains patient privacy, confidentiality and data protection at all times. The protection of data is regulated in accordance with Regulation (EU) 2016/679, and Organic Law 3/2018, and Law 41/2002.[26–28] Prior to their inclusion in the study, informed consent was obtained from all patients with asthma and their legal representatives in the case of minors. The project was approved by the Ethics Committee of the Hospital Universitario de Toledo (ethics approval number 1140) and subsequently by all the Ethics Committees of the participating hospitals.

Acknowledgments

The authors would like to thank all the medical and nursing teams of all participating Allergy and Pneumology departments for their continuous collaboration, dedication, and support throughout the development of this multicenter project. Their contribution to data collection, patient assessment, and coordination across centers was essential for the completion of this study. We also wish to acknowledge the support of Fundación Biotyc for their assistance with the publication process.

Author Contributions

All authors have made substantial contribution to the work described in this article, including conception, design, execution, acquisition of data, analysis and interpretation, or all of these; have been involved in drafting, revising, or critically reviewing the article; have given final approval of the version to be published; have agreed on the journal to which the article will be submitted; and agree to take responsibility for all aspects of the work.

Funding

This study had no private funding. With the support of Fundación Biotyc for publication. Fundación Biotyc was not involved in the design of the study, in the collection, analysis, and interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Disclosure

AMF reports honoraria for consultancy and conferences from Allergy Therapeutics, Asacpharma, AstraZeneca, Chiesi, GlaxoSmithKline, and Sanofi; research/training support from DIATER and FAES Farma; and assistance with travel to meeting from Letipharma and Roxall. MMMM reports honoraria for consultancy and conferences from AstraZeneca, GlaxoSmithKline and Sanofi. FMPB reports honoraria for conferences from AstraZeneca, GlaxoSmithKline and Sanofi. AMA has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis and Sanofi and has received speaker fees from AstraZeneca, GlaxoSmithKline, Novartis and Sanofi. AMEO reports honoraria for conferences from AstraZeneca, GlaxoSmithKline and Sanofi. MJL reports honoraria for conferences from AstraZeneca and GlaxoSmithKline. MJEM reports honoraria for consultancy and conferences from AstraZeneca, GlaxoSmithKline, and Sanofi. JBN reports non-financial support from Sanofi, during the conduct of the study; personal fees from Sanofi, personal fees from GSK, personal fees from AstraZeneca, outside the submitted work. MJA reports non-financial support from SANOFI, during the conduct of the study; personal fees from SANOFI, personal fees from GSK, personal fees from AstraZeneca, outside the submitted work. The remaining authors declare that they have no conflicts of interest.

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