Efficacy of Dupilumab for Severe Atopic Dermatitis Co-occurring With Asthma in a Real-World Setting

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Atopic dermatitis (AD) is a heterogenous relapsing chronic inflammatory disease with wide variations in its clinical presentation and severity. Severe AD (SAD) is characterized by recurrent eczematous plaques and severe itching, often associated with an increased risk for other atopic conditions (such as asthma) and mental health disorders [1,2]. Guidelines recommend conventional treatments as the cornerstone of therapy. Refractory cases can be treated with topical treatment and systemic immunosuppressants, and new targeted therapies have recently been approved or are in clinical development [3]. Dupilumab is the first biological agent approved for SAD that has proven effective, fast, and safe in affected patients [4]. It has proven efficacious in uncontrolled severe type 2 (T2) asthma by blocking the α subunit of the interleukin 4 receptor [5,6]. Receptor blockade remains stable for 4 weeks after administration [7]. However, little is known about its effect on asthma outcomes in patients with SAD and comorbid T2 asthma. The aim of this study was to describe the impact of dupilumab on asthma outcomes in adults with SAD and comorbid asthma.

We performed a retrospective observational study at La Paz University Hospital in Madrid, Spain. The local ethics committee approved the study (PI-5027). We included patients aged ≥18 years if they were receiving dupilumab for SAD at the standard dose (300 mg/2 wk) for at least 6 months and concomitantly presented objectively confirmed T2 asthma of any severity. General demographic data were recorded. Asthma control was classified before and ≥6 months after starting treatment, according to the Global Initiative for Asthma (GINA) guidelines, as well-controlled, partially controlled, and poorly controlled [8]. The results of lung function tests and

the Asthma Control Test (ACT) were recorded when available. Several scales for control and quality of life in SAD were evaluated, including SCORing Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Investigator Global Assessment, body surface area, and Dermatology Life Quality Index (DLQI). Blood eosinophil counts in peripheral blood and total serum immunoglobulin E (IgE) were also recorded. We analyzed data using the statistical program SAS 9.3 (SAS Institute). Quantitative data were expressed as median and interquartile range owing to their distribution. A *P* value <.05 was considered statistically significant.

Thirteen patients with SAD and asthma were included. Seven were men, and the median age was 35.7 years (range, 18-58). One patient had mild asthma, 11 moderate asthma, and 1 severe asthma. Allergic rhinitis (AR) co-occurred in approximately 75%-80% of all patients with asthma. While data on the effects of dupilumab in AR are lacking, the drug has been shown to improve asthma and significantly decrease the nasal symptoms associated with AR [6]. In our study, the most frequent related comorbidities were rhinitis (61.5%) and food allergy (30.8%). We have follow-up data after dupilumab for 6 of the 8 patients with rhinitis. Rhinitis improved in 5 of these patients, with fewer symptoms and less frequent use of topical and oral medication (no specific questionnaire was administered).

We do not have information on the progress of food allergies in the 4 affected patients, mainly because they avoid the foods. None of them were smokers or had gastroesophageal reflux, nasal polyposis, or obesity. Most patients experienced a marked clinical improvement in both diseases: 92.3% in AD and 61.5% in asthma. Only 1 patient presented well-controlled asthma before dupilumab. Asthma was controlled in 9 patients, and 6 of these patients reduced their GINA treatment step after ≥6 months of treatment. The ACT scores in the 5 patients with recorded data increased to 20, and asthma was completely controlled (ACT 25) in 4. Three patients presented conjunctivitis, the most frequent adverse event, 1 presented reactivation of herpes simplex, and none reported arthralgia or headache. In 1 patient, dupilumab was removed because of lack of efficacy in SAD. Values for SAD improved, and the differences were statistically significant (Table). There were also significant reductions in eosinophil counts and total IgE. Spirometry values for FEV_1 (percent predicted) and FEV_1/FVC increased, and a numerical improvement was recorded for all median z-scores in the before-and-after comparison (Table). FeNO was not evaluated.

Dupilumab is indicated for SAD in patients aged ≥12 years who are candidates for systemic therapy. However, the European Public Assessment Report provides no information regarding the use of dupilumab in SAD and comorbid asthma [9]. Very few clinical studies assess this topic. Boguniewicz et al [10] evaluated the impact of dupilumab on asthma and sinonasal conditions in adult patients with moderate-to-severe AD in 4 phase 3, randomized, double-blinded, placebo-controlled trials. Dupilumab improved all 3 diseases in a clinically meaningful and statistically significant manner. Of 2444 patients, 774 had asthma, although its severity was not evaluated. Asthma outcomes were assessed using the Asthma Control Questionnaire-5. Despite the large sample, the study was not performed under real-world conditions. The investigators documented comorbid asthma based on medical records rather than on objective diagnostic tests, and no pulmonary function data were obtained. We studied patients in a real-world setting, and asthma was diagnosed objectively and classified according to severity. Although pretreatment ACT was not recorded, post-ACT values reflect optimal asthma control in most cases; this was also reflected in the ability to

Table. Clinical Data of the Patients Included in the Study at Baseline and After Treatment.

Variable	Before treatment, median (IQR)	≥6 Months after, median (IQR)	*P* Value[a]
SCORAD (0-103)	64.50 (44.25-72.25)	19.40 (14.50-32.42)	.043
EASI (0-72)	25 (22-30)	3 (1-6.5)	.003
IGA (0-4)	4 (3-4)	1 (1-1)	.007
BSA (0-100)	41.50 (39.13-72.50)	5 (4-10)	.018
DLQI (0-30)	19.50 (13.75-23.25)	6 (1-6)	.027
Eos in blood, %	10.70 (6.55-15.30)	7.15 (3.80-8.43)	.049
Total IgE, kU/L	1196 (486-44375)	108 (57.65-6977)	.043
FEV_1, % predicted	96.45 (91.80-105.93)	101.50 (97.75-103.75)	NA
FEV_1, z-score	0.145 (–1.339 to 1.058)	0.039 (–0.167 to 0.206)	NA
FVC, % predicted	110.40 (106.88-112.60)	99 (96.75-107.25)	NA
FVC, z-score	1.260 (–1.662 to 1.706)	0.196 (–0.053 to 0.617)	NA
FEV_1/FVC, %	78.09 (73-82.50)	79.78 (78.81-85.57)	NA
FEV_1/FVC, z-score	–0.650 (–1.558 to 0.523)	–0.404 (–0.816 to 0.067)	NA

Abbreviations: BSA, body surface area; DQLI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Eos, eosinophils; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; NA, not analyzed; SCORAD, SCORing Atopic Dermatitis.
[a]Statistical significance was set at *P*<.05.

step down inhaled treatment and the improvement in asthma control according to the GINA recommendations.

Published experience on real-world scenarios is limited to 3 case reports of patients with SAD and asthma. One involved a 24-year-old man whose AD-related quality of life (EASI and DLQI) improved with dupilumab, as did his uncontrolled moderate asthma (ACT increased from 14 to 24) [11]. In another case report, EASI and the annual exacerbation rate decreased after 1 year of dupilumab in a 57-year-old Japanese woman with SAD and severe asthma [12]. Finally, the condition of a 35-year-old woman improved after 16 weeks of treatment with dupilumab (EASI and DLQI for SAD and FEV_1/FVC for asthma from 50% to 74%), and her diurnal symptoms became infrequent, nocturnal awakenings ceased, and IgE levels dropped [13]. Remarkably, these cases did not evaluate the same outcomes or have similar follow-up periods.

In conclusion, to the best of our knowledge, this is the largest population in which dupilumab administered to treat T2 inflammation in patients with SAD and comorbid asthma has improved both diseases simultaneously in a real-world setting and with validated measurements of asthma outcomes. However, as this is a retrospective, uncontrolled study with known limitations, further evaluation of these results in larger prospective, controlled, double-blind studies is needed.

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Conflicts of Interest

Katherine Pose and Daniel Laorden have received funding to attend congresses and conferences. Javier Domínguez Ortega has been an advisor, speaker, and investigator for AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Teva, LETI Pharma, and Sanofi. Santiago Quirce has been on advisory boards and has received speaker's honoraria from AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Mundipharma, Teva, and Sanofi. Natalia Hernandez has been on advisory boards and has received speaker's honoraria from Sanofi, AbbVie, and Leo Pharma. Elena Villamañán declares that she has no conflicts of interest.

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