Concomitant Efficacy of Dupilumab in Treating Eosinophilic Esophagitis and Type 2 Asthma

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Eosinophilic esophagitis (EoE) is a chronic, immune-mediated esophageal disease characterized by symptoms of esophageal dysfunction caused by eosinophilic inflammation. Diagnosis is based on the sum of symptoms of esophageal dysfunction, and an eosinophil count ≥15 per high-power field (HPF) on esophageal biopsy after exclusion of other causes of esophageal eosinophilia [1].

Dupilumab (Dupixent) is a fully human monoclonal antibody that blocks interleukin (IL) 4 and IL-13 signaling. It has been approved in Spain for severe atopic dermatitis (SAD) and severe asthma with a type 2 phenotype (T2-SA), whether associated or not with chronic rhinosinusitis with nasal polyps (CRSwNP). Based on published evidence, it has been approved by the United States Food and Drug Administration and the European Medicines Agency for the treatment of EoE. However, it is not currently available in Spain for EoE. The recommended dosage is 300 mg/2 wk, although this can vary. In EoE, the dose is 300 mg weekly for severe asthma [2]. Given that EoE belongs to the spectrum of T2-inflammatory diseases, we hypothesize that dupilumab would have concomitant beneficial effects on outcomes of EoE, even at doses lower than those approved by the regulatory agencies.

Our main objective was to assess responses in clinical outcomes, endoscopy (macro- and microscopic findings in esophageal biopsy specimens), and quality of life related to EoE. This multicenter retrospective observational study from a cases series involved 4 hospitals from throughout Spain. We included asthma patients aged ≥18 years who had been receiving dupilumab for T2-SA and/or SAD at the standard dose (300 mg/2 wk) for at least 6 months and had been objectively diagnosed with concomitant EoE. The Ethics Committee at La Paz University Hospital in Madrid approved the study (PI-5705). A clinical response to EoE was defined as a objective decrease in the number and intensity of symptoms (choking, impaction, dysphagia, chest pain, and gastroesophageal reflux symptoms) and an improvement in patient-reported quality of life questionnaire scores. Meanwhile, histopathological improvement was evaluated using esophagoscopy, with improved macroscopic response in the endoscopic reference score questionnaire and a reduction in eosinophil counts (<15/HPF) in the biopsy specimen.

Nine asthma patients were included, 2 with mild disease, 1 with moderate disease, and 6 with SA. Five were men, and the median (IQR) age was 40 (17-59) years. Allergic rhinoconjunctivitis co-occurred in 8 patients, CRSwNP in 4, and SAD in 4. The median age at onset of esophagitis was 31.11 (16-54) years.

Before receiving dupilumab, 5 patients had been treated with oral corticosteroids for SA, and 3 had been treated with benralizumab, omalizumab, or mepolizumab for asthma. Two patients had received cyclosporine and another 2 had received calcineurin inhibitors for SAD.

Most patients with SA (8/9) had an allergic/inflammatory phenotype, and 1 had a mixed phenotype.

Symptoms and histopathology findings improved in patients who had undergone esophagoscopy after being treated with dupilumab for ≥6 months. In addition, the results of the Adult EoE Quality of Life Questionnaire revealed improved quality of life. The most relevant results are shown in the Table. All patients were able to completely withdraw treatment with oral corticosteroids and/or immunosuppressants.

It is not uncommon for T2-SA patients to have a history of comorbid T2 conditions. Dupilumab is indicated for T2-SA patients aged ≥12 years and for CRSwNP, SAD, and EoE. The GINA guidelines expressly recommend the use of dupilumab in SA patients with concomitant SAD [2], although no similar proposals have been made for SA and coexisting EoE, particularly since dosages differ between the diseases (weekly in the case of EoE) [3]. In fact, dupilumab reduced levels of type 2 biomarkers in randomized placebo-controlled trials in patients with SAD, asthma, CRSwNP, and EoE [4], with decreasing total IgE levels in all indications and more varied blood eosinophil responses. Moreover, while rarely clinically relevant, we observed no transient increases in peripheral eosinophil counts in this cohort of SA and EoE patients.

Table. Patient Data at Baseline and ≥6 Months of Treatment.[a]

	Before treatment	≥6 Months
Dysphagia, No.	9	0
Impactation, No.	4	0
Chest pain, No.	5	0
Gastroesophageal reflux, No.	7	3
PPI treatment, No.	6	3
SCT, No.	3	0
ED, No.	2	1
Without treatment (PPI, SCT, ED) at start of dupilumab treatment	3	8
With treatment (PPI, SCT, ED) at start of dupilumab treatment	6 (3 with PPI and SCT; 1 with PPI; 2 with ED and PPI)	1 (with PPI)
Mean (SD) EREFS	4.55 (2.35) Median, 5-9 patients	1.75 (0.95) Median, 1.5-4 patients
Mean (SD) eos/HPF in upper third	45 (37) 9 patients	0 4 patients
Mean (SD) eos/HPF in lower third	74 (41) 9 patients	5.75 (9) 4 patients
Mean (SD) blood eosinophil counts	547 (419)	518 (365)
Mean (SD) % blood peripheral eosinophils	6.99 (5.9)	7.34 (5)
Mean (SD) IgE, IU/mL	1691 (1533) Median 1558)	945 (1797) Median 325
Mean (SD) FeNO, ppb	76 (69)	18 (3)
Mean (SD) FEV_1, %	88 (17)	86 (9)
ELSA score 5 patients	21.1	9.8
EoE-QoL-A 4 patients	71	35
ACT	15 (4.69)	21.5 (1.04)

Abbreviations: ACT, Asthma Control Test; ED, exclusion diet; ELSA, Esophagitis Live Symptoms Assessment; EoE-QoL-A, Adult Eosinophilic Esophagitis Quality of Life Questionnaire; eos, eosinophils; EREFS, endoscopic reference score questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; HPF, high-power field; IgE, immunoglobulin E; PPI, proton pump inhibitors; SCT, swallowed corticosteroid treatment.
[a]All patients were administered dupilumab at a dose of 300 mg every 2 weeks.

Published experiences from real-world scenarios are lacking. Isolated cases in children have previously demonstrated the efficacy of dupilumab on EoE outcomes and SAD [5]. Colque-Bayona et al [6] recently reported a single case of an adult with several T_H2 inflammatory conditions (EoE, SAD, SA, and CRSwNP) and a good clinical and histological response after treatment with dupilumab at the doses indicated for asthma and atopic dermatitis. The largest cohort to date, which reported data from 11 children with SA treated with dupilumab [7] in a larger study of 45 patients with EoE taking dupilumab for other T2 conditions, indicated that the drug could be administered for moderate-to-severe conditions or compassionate use. The authors observed a significant improvement in symptoms in 28 patients, with 24 patients reporting complete resolution of symptoms after initiation of dupilumab. Histologic data were available for 26 patients, of whom 22 had fewer than 6 eosinophils per HPF after initiation of biologic treatment. In asthma patients, the number of exacerbations requiring oral corticosteroids decreased significantly from 12 in the 6 months preceding dupilumab to 2 in the first 6 months after treatment, and the Asthma Control Test scores improved 7 points globally up to a mean of 22.7 (2.1). However, there were no specific data for outcomes of EoE. Moreover, since allergic SA is more prevalent in childhood, the results may have been influenced by a bias arising from overselection of more atopic and less fibrotic EoE than in the population we studied. Nevertheless, based on our data, it is unclear whether dupilumab would work as a single agent administered twice weekly, since most patients were undergoing concurrent treatment with exclusion diets, proton pump inhibitors, and/or swallowed corticosteroids. Only 3 patients were not receiving treatment at initiation of dupilumab. Even so, all 3 were able to stop swallowed corticosteroids, reduce the proton pump inhibitor dose, and be more lax with their exclusion diets.

Since this is a retrospective, uncontrolled study with known limitations, further evaluation of the results in larger, prospective, double-blind, controlled studies is necessary to facilitate personalized medical therapy. In conclusion, to our knowledge, this is the largest adult population in which the administration of dupilumab at 300 mg/2 wk has simultaneously improved both a T2 condition including asthma and comorbid EoE, as demonstrated by validated measurements of clinical and histological outcomes in a real-world setting.

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Conflicts of Interest

Margarita Tomás Pérez has received speaker's honoraria from Inmunotek, ALK, and Allergopharma and fees for attending meetings and/or travel from Roxall and LETI Pharma.

Javier Dominguez-Ortega has participated on advisory boards and received speaker's honoraria from AstraZeneca, Teva, Novartis, GSK, Sanofi Genzyme, Chiesi, Allergy Therapeutics, LETI Pharma, and ALK-Abelló.

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Andrea Trisán Alonso has participated on advisory boards and received speaker's honoraria from GSK, AstraZeneca, Sanofi, and Chiesi.

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Miriam Clar Castelló declares that she has no conflicts of interest.

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