

Concomitant Efficacy of Dupilumab for severe atopic dermatitis and comorbid asthma in real-life conditions

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Atopic dermatitis (AD) is a heterogeneous relapsing chronic inflammatory disease, with a wide variation of 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 AD therapy. For refractory cases to adequate topical treatment, there are systemic immunosuppressive therapies and, more recently, new targeted therapies have been approved or are in clinical development [3]. Dupilumab is the first biological agent approved to treat SAD that resulted in being effective, fast and safe in these patients [4]. Dupilumab has also shown efficacy in uncontrolled severe Type-2(T2) asthma by blocking the alpha-subunit of the interleukin-4 receptor [5,6]. Receptor blockade remains stable for the next 4 weeks after administration [7]. However, there is a lack of information regarding its effect on asthma outcomes in patients with SAD and comorbid T2-asthma. The aim of this study is to describe the impact of dupilumab on asthma outcomes in adults with SAD and comorbid asthma.

We present a retrospective observational study carried out at La Paz University Hospital in Madrid (Spain). The local Ethics Committee approved the study (PI-5027). We included patients ≥ 18 -year-old were included if they were on treatment with dupilumab for SAD at standard dose (300 mg/2

weeks) for at least six months, and concomitantly presented objectively confirmed type-2 asthma of any severity. General demographic data was registered. Asthma control was classified before and ≥ 6 months after starting treatment, according to Global Initiative for Asthma (GINA) guidelines as well-controlled, partially controlled, and poorly controlled [8]. Lung function tests and asthma control test (ACT) were also 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 (IGA), Body Surface Area (BSA) and Dermatology Life Quality Index (DLQI). Blood eosinophils counts in peripheral blood and total serum immunoglobulin E (IgE) were also registered. We analyzed data with the statistical program SAS 9.3 (SAS Institute, Cary, NC, USA). Quantitative data was described using the median and interquartile range, due to the distribution of these data. A p-value < 0.05 was considered statistically significant.

Thirteen patients with SAD and asthma were included. Seven were men, median age 35.7 years (range from 18 to 58 yrs.). One patient had mild asthma, eleven moderate asthma and one severe asthma. Allergic rhinitis (AR) co-occurs in nearly 75%-80% of all patients with asthma. There are very few studies on the effects of dupilumab in AR, but they did result in improvement in asthma and a significant decrease in nasal symptoms associated with AR [6]. In our study, the most frequent related comorbidities were rhinitis (61.5%) and food allergy (30.8%). Of the 8 patients with rhinitis, we have follow-up data after dupilumab in 6 of them, 5 of whom have shown improvement in their rhinitis, with fewer symptoms and less 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 patients who presented it, mainly because they avoid those foods. None of them were smokers or presented with 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 while nine had their asthma controlled and 6 out of 9 patients stepped-down GINA treatment step after ≥ 6 months of treatment. ACT scores in the 5 patients with recorded data increased up to 20, with 4 of them reflecting complete asthma control (ACT 25). Three patients presented conjunctivitis, the most frequent adverse event, one presented herpes simplex reactivation, and none reported arthralgia or headache. In one patient, dupilumab was removed because of lack of efficacy in SAD outcomes. SAD scales improved with statistical significance (table 1 and Figure 1 for EASI). There were also significant reductions in the counts of eosinophils and total IgE. An increase in spirometry values for FEV₁ (percent predicted) and FEV₁/FVC was observed, and all median z-scores showed numerical improvement in the before-and-after comparison (Table 1). FeNO was not evaluated.

Dupilumab is indicated to treat SAD in patients ≥ 12 years of age 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]. There are very few clinical observations assessing this topic. Boguniewicz *et al.* evaluated the impact of dupilumab on asthma and sinonasal conditions in adult patients with moderate-to-severe AD in four phase 3, randomized, double-blinded, placebo-controlled trials⁹. Dupilumab improved all three diseases in a clinically meaningful and statistically significant manner [10]. From 2,444 patients, 774 had asthma, but its severity was not evaluated. Regarding asthma outcomes, Asthma Control Questionnaire-5 was measured. Although many patients were recruited, it was not a real-life study. Investigators documented comorbid asthma based on medical records rather than objective diagnostic tests, and no pulmonary function data were obtained. We studied patients in a real-life setting and asthma was objectively diagnosed and classified according to severity. Although pre-treatment ACT was not recorded, post-ACT values

reflect an optimal asthma control in most cases, which also is reflected in the capacity of stepping down in inhaled treatment and improvement in asthma control according to GINA recommendations.

Considering real-life scenarios, there is much less published experience, and it is limited to three case reports of patients with SAD and asthma. One presented a 24-year-old who improved the AD-related quality of life (EASI and DLQI) with the use of dupilumab but also improved her uncontrolled moderate asthma (ACT increased from 14 to 24) after treatment [11]. Another case report of a 57-year-old Japanese woman with SAD and severe asthma after one year of dupilumab treatment decreased EASI and the annual exacerbation rate [12]. Finally, a 35-year-old woman who improved after sixteen weeks treatment with dupilumab (EASI and DLQI for SAD and FEV1/FVC for asthma from 50% to 74%) while diurnal symptoms became infrequent, nocturnal awakenings ceased and IgE levels dropped [13]. Remarkably, these cases did not evaluate the same outcomes, nor considered the same time of follow-up.

In conclusion, to the best of our knowledge, this is the largest population in which dupilumab, targeting type-2 inflammation in patients with SAD and comorbid asthma, has improved both diseases concomitantly in a real-life setting and with validated measurements of asthma outcomes. However, as this is a retrospective, uncontrolled study with its known limitations, further evaluation of these results in larger prospective, controlled, double-blind studies is needed.

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CONFLICTS OF INTEREST

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Table 1. Clinical data of the patients included in the study at baseline and after treatment.

| Variable | Before treatment, median (P25-P75) | ≥ 6 months after, median (P25-P75) | p value |
|--------------------------------------|------------------------------------|------------------------------------|------------------|
| SCORAD (0-103) | 64.50 (44.25 - 72.25) | 19.40 (14.50 - 32.42) | p = 0.043 |
| EASI (0-72) | 25 (22 - 30) | 3 (1 - 6.5) | p = 0.003 |
| IGA (0-4) | 4 (3 - 4) | 1 (1 - 1) | p = 0.007 |
| BSA (0-100) | 41.50 (39.13 - 72.50) | 5 (4 - 10) | p = 0.018 |
| DLQI (0-30) | 19.50 (13.75 - 23.25) | 6 (1 - 6) | p = 0.027 |
| Eos in blood (%) | 10.70 (6.55 - 15.30) | 7.15 (3.80 - 8.43) | p = 0.049 |
| Total IgE (kU/L) | 1196 (486 - 44375) | 108 (57.65 - 6977) | p = 0.043 |
| FEV₁ (% predicted) | 96.45 (91.80 - 105.93) | 101.50 (97.75 - 103.75) | NA |
| FEV₁ (z-score) | 0.145 (-1.339 - 1,058) | 0.039 (-0.167 - 0.206) | NA |
| FVC (% predicted) | 110.40 (106.88 - 112.60) | 99 (96.75 - 107.25) | NA |
| FVC (z-score) | 1.260 (-1.662 - 1.706) | 0.196 (-0.053 - 0.617) | NA |
| FEV₁/FVC (%) | 78.09 (73 - 82.50) | 79.78 (78.81 - 85.57) | NA |
| FEV₁/FVC (z-score) | -0.650 (-1.558 - 0.523) | -0.404 (-0.816 - -0.067) | NA |

Abbreviations: SCORAD, Scoring Atopic Dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; Eo, eosinophils; IgE, immunoglobulin E; FEV₁, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; NA, non-analyzed; P value <0.05 expresses statistical significance; P25-P75, percentile 25-75.