

52 WEEK FOLLOW-UP SAFETY AND EFFECTIVENESS RESULTS OF DUPILUMAB TREATMENT OF MODERATE TO SEVERE ATOPIC DERMATITIS FROM A RETROSPECTIVE, MULTICENTRIC SERIES.

Abstract

Atopic dermatitis (AD) is a chronic, systemic disease that has a multifactorial etiology, where immune system disorders and epidermal barrier dysfunction are added to the influence of genetic and environmental factors. Dupilumab has been approved by US and EU regulatory agencies in 2017 for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic treatment. In this short report, we present a retrospective, multicentric study, in which five hospitals in Andalusia, Spain, have taken part. Our objective is to evaluate the safety and effectiveness of dupilumab in patients with moderate to severe AD treated with Dupilumab with at least 52 weeks of follow up.

Atopic dermatitis (AD) is a multifactorial, pruritic disease resulting from the interaction of genetic disposition and environmental triggers with a marked skin barrier dysfunction and a Type 2 (T2)-driven immune dysregulation (Guttman-Yassky E, 2018). Although the dysfunction of the cutaneous barrier and the immune alteration are the main disorders in these patients, the causality of this relationship is not known accurately. AD usually starts in early infancy, evolve with a recurrent course before disappearing at adolescence, though it may persevere to adulthood or present de novo during this period (Silvestre Salvador JF, 2017).

AD is moderate-to-severe in around one third of patients, for whom therapeutic approach can be challenging beyond topical treatments, as phototherapy and/or systemic therapies often do not guarantee adequate control of the disease or acceptable safety profile (Silverberg JI, 2017; Boguniewicz M, 2017).

Dupilumab is a fully human monoclonal antibody that targets the common IL-4 receptor α (IL-4 R α), blocking both IL-4 and IL-13 signaling. Dupilumab is the first targeted therapy approved by the FDA and EMA for the treatment of moderate-to-severe AD in adults, and has shown to be effective to control the signs and symptoms of AD in previous clinical trials (Serra-Baldrich E, 2018; Beck LA, 2014; Simpson EL, 2016; Thaçi D, 2016; Simpson EL, 2016; Blauvelt A, 2017; de Bruin-Weller M, 2018). Its compassionate use has recently been approved in our country.

As real world evidence publications with dupilumab are limited to date (Ruiz Villaverde, 2019, Faiz S, 2019), so it is necessary to assess the performance of this treatment in real clinical practice, both in the short and long-term follow up.

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We present a series of 30 patients from 5 Andalusian hospitals included in the Spanish compassionate use program of Dupilumab for adult patients with moderate to severe AD, between October 2017 and May 2018. Patients had a diagnosis of AD, confirmed by an experienced dermatologist of one of the participating reference hospitals. Table 1 shows demographic and clinical characteristics such as age, time of evolution of the disease, personal history (including comorbidities), and previous systemic/biological treatments, recorded from patients included in this series at baseline visit. Disease severity was measured by SCORing Atopic Dermatitis (SCORAD) and Pruritus Visual Analogue Scale (VAS) scores at baseline visit, and at weeks 4, 12, 24 and 52. Quality of life was assessed with Dermatology Life Quality Index (DLQI). Dupilumab was prescribed following the approved dosage: initial dose of 600 mg and then 300 mg every 2 weeks.

This retrospective study was conducted in full compliance with the regulations for compassionate use programs established by the Spanish Medicines and Medical Products Agency (Agencia Española del Medicamento y Productos Sanitarios, AEMPS). Patients included in the expanded access program were provided with an informed consent.

The included population presented a significant burden of disease, with an average of 25.7 years of AD evolution. The most frequent comorbidities were allergic rhinitis (55.5%), extrinsic asthma (37%) and conjunctivitis (33.4%). All patients had received previous treatment with oral corticosteroids, and 96.3% had been treated with cyclosporine.

The effectivity of dupilumab treatment was assessed at weeks 4, 12, 24 and 52. Mean change in SCORAD is shown in Fig. 1, while DLQI evolution is shown in fig. 2. Regarding the effectiveness of dupilumab treatment, at baseline the mean SCORAD was 59.4, while the pruritus VAS was 8.3. At the follow-up week 52 visit, SCORAD decreased to 10.5 (82.3%) and pruritus VAS reduced to 2.1 (74.7%). Regarding quality of life, baseline DLQI was 19, reaching a score of 2 (89.5%) at the same cut-off.

Concomitant treatment was prescribed according to clinical decision by the investigators. Topical corticosteroids were used in 10 patients at baseline, maintaining their use to week 52 in 4 cases. Antihistamines use also diminished from 4 to 2 patients during follow-up. Oral corticosteroids were prescribed to 5 patients at baseline, being necessary in 1 case at week 52. At baseline, 2 patients were treated with concomitant methotrexate, and another with mofetil mycophenolate, which were progressively suspended.

The most common adverse event (AE) was conjunctivitis, with 5 (16.6%) cases reported. All cases were transitory, and managed successfully without dupilumab withdrawal. Other AEs reported were cheilitis, mild AD flare, unilateral gynecomastia, and canker sores, all transitory and managed without dupilumab withdrawal.

The clinical safety and effectiveness of dupilumab in our series were consistent with those observed in clinical trials (Beck LA, 2014; Simpson EL, 2016; Thaçi D, 2016; Simpson EL, 2016; Blauvelt A, 2017; de Bruin-Weller M, 2018). Dupilumab significantly improved the signs and symptoms of AD, measured by SCORAD and pruritus VAS, as well as QoL. We have observed that maximum effectivity was reached at week 24, which is slightly later than what was reported in clinical trials. We have extended our experience from previous publications up to 52 weeks, observing a maintenance of the response and no emerging or

unpredicted adverse events. Recently, another real clinical practice series of AD patients treated with dupilumab has been reported, showing significantly higher incidence of conjunctivitis (Faiz S, 2019). As our experience appears to be different, further studies on the causes of conjunctivitis with dupilumab should bring us light on its possible, but ambiguous interconnection, as this adverse event was not reported in studies of dupilumab for other indications, including nasal polyposis and asthma, and may be unique to the atopic dermatitis population.

In this series, dupilumab has shown a favorable effectivity and safety profile, especially in this long evolution, multi-failure, difficult-to-treat population. The presence of comorbidities was also a remarkable severity characteristic of this sample. We would also like to highlight, from the safety analysis, the maintenance of a favorable safety profile during the 52 weeks follow-up, remarking the absence of cutaneous infections or herpes. The incidence of ocular disorders in our series was low, and seems to appear early once the treatment was initiated. Another promising outcome is the absence of treatment withdrawal, neither for lack of efficacy nor for adverse effects.

The value provided by this multicenter, retrospective study lies in the need of real clinical practice data of new treatments targeting severe AD, as our knowledge is limited up to now. The limitations of this study are the small size of the sample and the short follow up period. Future studies should assess the real clinical practice response to dupilumab in broader population with longer follow-up periods. Further research should bring light about the different patterns of response to treatment according to different phenotypes, as atopic dermatitis is a tremendously heterogeneous pathology.

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Table 1. Baseline characteristics:

Variable	Value
Age (years)	42.11 (19-64)
Male (gender)	70.37 males (19/27)
Average time of evolution of AD (years)	25.70 years (3-44 ys)
Comorbidities (%)	
Nasal polyposis	14.81%
Conjunctivitis	33.38%
Extrinsic bronchial asthma	37.03%
Allergic rhinitis	55.55%
Food allergies	22.22%
Previous treatments	
Systemic corticosteroids	100%
Oral cyclosporine	96.29%
Phototherapy (UVBBE)	40.74%
Methotrexate	37.03%
Azathioprine	44.44%
MMF	14.80%
Immunoglobulins ivs	29.62%

Fig. 1. SCORAD evolution from baseline trough week 52

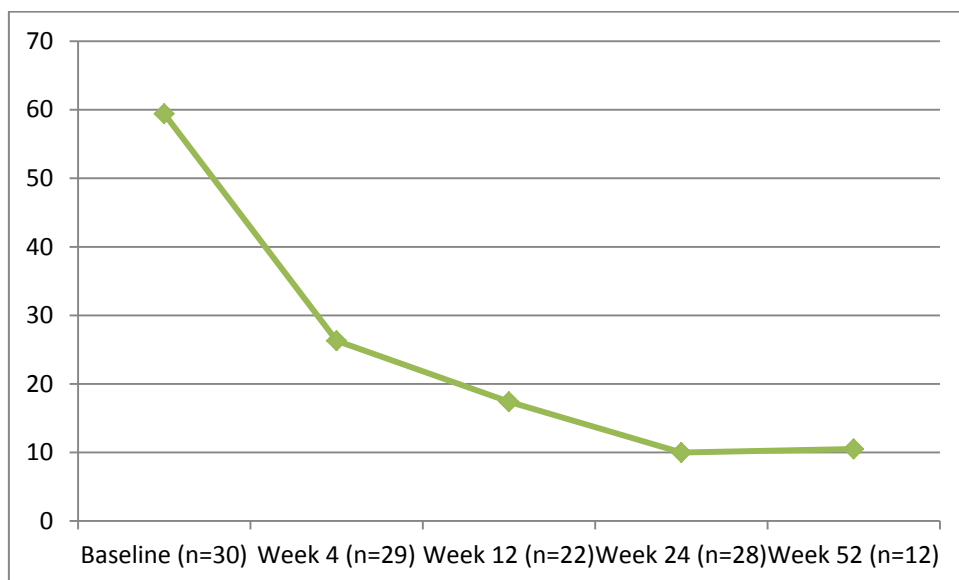


Fig. 2. DLQI evolution from baseline trough week 52

