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Article

Patient Reported Outcome Measure in Atopic Dermatitis Patients treated with Dupilumab: 52-Weeks results

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Abstract: Dupilumab is used to treat atopic dermatitis patients who have proven to be refractory to previous treatments. The aim of this study was to assess evolution and patient reported outcome measures in adult patients with moderate-to-severe atopic dermatitis treated with Dupilumab in routine clinical practice. The outcomes were evaluated and registered at baseline and weeks-16, 40 and 52. The variables evaluated were: diseases severity, pruritus, stressful life events, difficulty to sleep, anxiety and depression, quality of life, satisfaction, adherence to the treatment, efficacy and safety. Eleven patients were recruited between Nov 14th 2017 and Jan 16th 2018. Demographic variables: 90% Caucasian, 82% women. Clinical variables: Mean duration of AD =17.7 (±12.8), 91% had severe disease severity. At baseline, SCORAD mean score = 61.7 (±15.5); itch was reported by 100% of patients; itch Visual Analogue Scale mean range of 8 (6-10); HADS mean total score =13.9 (±5.5); DLQI mean score =13.3 (±8.3): EQ-5D-3L mean range = 57 (30-99). At week-52 there is a significant reduction of SCORAD scores, HADS total score and improved quality of life. ¡This study confirms that Dupilumab, used for 52-weeks under routine clinical practice, maintains the improved atopic dermatitis signs and symptoms obtained at week-16, with a good safety profile.

Keywords: Atopic dermatitis; Patient Reported Outcome Measures; Dupilumab; Quality of life; Satisfaction; Efficacy; Safety; Adherence

1. Introduction

Atopic dermatitis (AD), a chronic inflammatory skin disease that evolves as flares, is characterized by itching and eczema. AD affects 2-10% of adults [1] and, in severe cases, is associated with significant psychosocial distress [2]. Moderate-to-severe AD requires long- term immunosuppressive therapy whose efficacy profile and long-term adverse effects are not clear [3-6]. Treatment guidelines recommend short-term high-strength topical corticosteroids with or without calcineurin inhibitors to control outbreaks, in addition to topical emollients [7,8]. Systemic treatment with corticosteroids or immunosuppressants (cyclosporine, methotrexate, azathioprine, etc.), and phototherapy,

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are indicated only in cases not controlled by topical treatment [9,10]. Long- term systemic treatments are not indicated due to their bad safety and efficacy profile [11,12].

Dupilumab is a human monoclonal antibody that specifically blocks the alpha receptor of interleukin-4 (IL-4), inhibiting interleukin-4 and interleukin-13 signaling of these inflammatory cytokines involved in various allergic diseases, such as asthma, atopic dermatitis and rhinitis [13]. Dupilumab has shown a good efficacy and safety profile in monotherapy or associated with topical corticosteroids [14-16]. It has been approved by the European Medicines Agency [17] for the treatment of moderate-to-severe AD in adult patients in whom systemic treatment is indicated.

Patient-reported outcome measure (PROMs) provide an important adjunct to clinician-assessed measures in atopic dermatitis [18].

The aim of this study is to assess evolution and PROMs in adult patients with moderate-to-severe atopic dermatitis treated with Dupilumab in routine clinical practice. Efficacy, safety, psychosocial impact, quality of life, adherence to treatment and satisfaction were the variables measured in adult patients with AD treated with subcutaneous dupilumab during 52 weeks. The analysis of preliminary data in week 16 were previously published [19]. We present definitive data up to week 52.

2. Materials and Methods

2.1. Study Group

This study included AD patients who met criteria for Dupilumab treatment in the dermatology department of the Royo Villanova Hospital, Zaragoza, Spain between November 14th 2017 and January 16th 2018. Treatment with dupilumab was possible through adherence to a program of extended medication use authorized by the Spanish Agency for Medicine and Health Products (AEMPS). The proyect identification code is NPP 14985 (015649). Date of approval: October 2017, by the AEMPS. All patients gave signed informed consent to be included in the program and authorized the use of the clinical data obtained. The hospital pharmacy service sends a request and individualized report on the patient to be included in the treatment program to AEMPS. Once authorization is obtained, the pharmaceutical company sends the medication for each patient to the pharmacy service for dispensation. Patients have to apply emollient creams twice a day after the baseline visit (request for inclusion). Once treatment has been authorized and the medication is available in the hospital pharmacy, treatment with dupilumab 300 mg subcutaneously every 2 weeks, with an initial loading dose of 600 mg on the first day, is administered. To prevent conjunctivitis, patients are recommended to use preventive artificial tears. The following face-to-face visits were included in the protocol: inclusion, treatment initiation (baseline visit), weeks 4,8,12,16 and then every 12 weeks (weeks 28,40 and 52). A Case Report Form (CRF)was completed for each treatment visit to guarantee data quality. The sociodemographic variables collected were: age, gender, education, family status and occupation. Other variables: stressors during the previous 6 months, height, weight and body mass index (BMI). Routine clinical demographic data included: age at onset of AD, years of evolution, patient-perceived severity in the last year and currently, and previous topical and systemic treatments administered. The study was carried out according to the provisions of the Helsinki Declaration and current Spanish legislation. All patients were evaluated and authorized individually by AEMPS; it is necessary to renew this authorization every 12 weeks for treatment to continue. The results analyzed were obtained during the baseline visit and at 16, 40 and 52 weeks of treatment.

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2.2. Outcome variables

In order to evaluate the influence of AD on patients' outcome variables, they were asked to complete: a) AD severity using the Scoring Atopic Dermatitis (SCORAD) index [20]; b) variables related to pruritus (stinging, burning or pain) and its negative impact on their relationships, sleep disturbance and mood; c) anxiety and depressive symptoms using the Hospital Anxiety and Depression Scale (HADS) [21]; d) quality of life using the EuroQol 5D-3L (EQ-5D-3L) [22] and the Dermatology Life Quality Index (DLQI) [23]; e) patient satisfaction using an "ad hoc" visual analogue scale (VAS) [24] and the Consumer Reports Effectiveness Scale (CRES-4) [25], which measures satisfaction with treatment; f) treatment adherence, checked by counting boxes and syringes consumed at each visit; g) safety; and h) adverse effects. The results are obtained from the analysis of the comparison at the baseline visit, and at 16, 40 and 52 weeks.

2.3. Statistical analysis

Qualitative variables are shown as frequencies and percentages and quantitative variables as mean, median, standard deviation (SD), maximum and minimum. VAS variables were considered discrete quantitative variables and the median and range were calculated. Comparisons were made between the 3 moments of ANOVA for repeated measures and Student's t test for related data when the variable was distributed normally or with the Friedman or Wilcoxon T tests when it was not. Normality was determined using the Kolmogorov Smirnov test. A value of p=0.05 was used as a threshold to accept or reject the null hypotheses; however, this p-value was 0.016 (0.05/3) to make the bivariate comparison between the three moments after rejecting the hypotheses of equality between the three moments. The data were analyzed using SPSS 25.0.

3. Results

The study group comprised 11 adult patients, 9 (81.8%) females; 6 (54.5%) had secondary studies and 5 (45.5%) had university studies; 8 lived with family (72.7%) and 3 (27.3%) alone; 3 were students (27.3%), 5 (45.5%) were active workers, 1 (9.1%) unemployed and 1 (9.1%) on sick leave; 5 patients (45.5%) reported having had stressful life events in the last 6 months. The mean age (± standard deviation, SD) was 33.2 ± 15.6 years with a median 24 and range (71.0-21.0), the mean weight was 72.0 ± 14.4 Kg with median 71.0 and range (99.0-53.0); median height was 165.9 ± 5.6 cm with median 167.0 and range (176.0-155.0); the mean body mass index (BMI) was 26.1 ± 4.5 with a median 25.5 and range (34.6-21.1). The mean number of years of illness was 16.6 ± 22.5 with a median 4.0 and range (66.0-1.0); the mean number of years of evolution was 17.7 ± 12.8 with a median 19.0 and range (44.0-1.0); SCORAD mean was 61.7 ± 15.5 with median 65.6 and range (86.1-66.0). A total of 10 (90.9%) patients manifested "severe" type and 1 (9.1%) "moderate" type. Regarding topical treatment, all patients received emollients two times a day and artificial tears; 8 patients (72.7%) with topical tacrolimus; 3 (27.3%) with Fusidic acid + betamethasone; 2 (18.2%) with Pimecrolimus; 2 with mupirocin. Regarding systematic treatment, 10 patients (90.9%) received prednisone; 5 (45.7%) with cyclosporine; 2 (18.2%) with photo therapy; 2 (18.2%) with methotrexate; 1 (9.1%) with Apremilast; 1 (9.1%) with dexchlorpheniramine / betamethasone; 1 (9.1%) with hydroxyzine; (54.5%) with Bilastine and 1 (9.15) with omeprazole.

3.1. Evolution of visits: baseline, 16, 40 and 52 weeks.

The evolution of the variables related to the symptoms are presented below in Table 1. Variables related to the evolution of quality of life or results perceived by patients are presented in Table 2. Variables related to safety are presented in Table 3, and variables

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related to satisfaction between current treatment with Dupilumab and previous treatment are presented in Table 4.

3.2. Comparative of symptoms analysis at baseline, 16, 40 and 52 weeks.

The following tables and figures present the comparison of the baseline visit with week 16, week 40 and week 52. Table 5 and Figures 1-3 show the evolution of the disease severity and symptoms, showing a decrease on disease severity (SCORAD Index) from (64.5 ± 19.6 to 5.5 ± 5.9, p<0.001) at week 16 that is maintained or even improved in weeks 40; (5.8 ± 5.7) and week 52; (5.3 ± 6.0). Regarding pruritus, a decrease is observed between the baseline visit and week 16 from 8 to 1, (p<000.1), that is maintained in week 40 and week 52, although a slightly higher value is observed in the itch in week 52 which was not statistically significant, (p=0.259). Regarding difficulty to sleep, a decrease is also observed at week 16 from 8 to 1 (<0.001), that shows a tendency to improve until it stops being a problen at week 44 and week 52.

3.3. Comparative self-perceived psychological and quality of life issues analysis at baseline, 16, 40 and 52 weeks.

Table 6 and Figures 4-8 show the evolution of quality of life, which improves at week 16 and remains unchanged until week 52.

HADS score fell by (9.2 ± 3.0 to 3.9 ± 3.4, p=0.007) at week 16 and continue decline at week 40 and week 52, (<0.001) and from depression (4,7 ± 3.4 to 1.9 ± 2.5, p=0.008) at week 16 and continue decline at week 40 and week 52, (<0.001). In the DLQI questionnaire (13.9 ± 8.3 to 2.0 ± 1.8, p=0.001) at week 16 and continue decline at week 40 and week 52, (<0.001). In the EQ-5D-3L VAS increases from 57 to 80, (p=0.035) at week 16 and continue increase during week 40 and week 52, (<0.001).

Table 7 presents the values of the safety variables and the comparison between them. The table shows that there are no statistically significant differences in SBP, DBP, pulse or body temperature.

3.4. Comparative satisfaction analysis at baseline, 16, 40 and 52 weeks.

The results of the comparison of satisfaction with the current treatment with the previous one at week 16 and week 40 with week 16 and 52 are presented in Table 8. Satisfaction increases from week 16, although there is a reduction in global satisfaction between weeks 40 and 52. This reduction is more statistical than clinical, the descriptive values are the same (median equal to 10), producing some difference in the range, which drops the minimum value from 7 to 4.

The values referred to the comparison of the CRES-4 score are presented inTable 9. It can be seen that there are no statistically significant differences between week 16, week 40 and week 52.

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Table 1. Symptom descriptions at baseline visits, 16, 40 and 52 weeks

Variable	Baseline	Week 16	Week 40	Week 52
Severity, n (%)				
Without lesions	0 (0.0)	3 (27.3)	2 (18.2)	4 (36.4)
Almost no lesions	0 (0.0	2 (18.2)	8 (72.7)	6 (54.5)
Mild	0 (0.0)	4 (36.4)	1 (9.1)	1 (9.1)
Moderate	0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)
Severe	11(100)	0 (0.0)	0 (0.0)	0 (0.0)
Weight, mean (SD)	74.7 (14.2)	74.0 (15.3)	75.4 (13.6)	75.0 (15.8)
BMI, mean (SD)	27.0 (4.4)	26.8 (4.9)	27.2 (4.2)	27.1 (5.0)
SCORAD, mean (SD)	64.5 (19.6)	5.5 (5.9)	5.8 (5.7)	5.3 (6.0)
Itching. Yes, n (%)	11 (100)	8 (72.7)	7 (63.6)	9 (81.8)
VAS pruritus, mean (range)	8 (10-6)	1 (6-0)	1 (4-0)	1 (6-0)
Pruritus, characteristics. Yes, n (%)				
Itching only	4 (36.4)	9 (81.8)	9 (81.8)	9 (81.8)
Burning	8 (72.7)	0 (0.0)	0 (0.0)	0 (0.0)
Stinging	8 (72.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	7 (63.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus, frequency. Yes, n (%)				
Never	0 (0.0)	2 (18.2)	1 (9.1)	2 (18.2)
Rarely	0 (0.0)	3 (27.3)	6 (54.5)	6 (54.5)
Sometimes	1 (9.1)	4 (36.4)	4 (36.4)	2 (18.2)
Often	5 (45.5)	2 (18.2)	0 (0.0)	1 (9.1)
Always	5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)
Unbearable itching, n (%)				
Never	0 (0.0)	6 (54.5)	7 (63.6)	7 (63.6)
Rarely	0 (0.0)	3 (27.3)	1 (9.1)	3 (27.3)
Sometimes	3 (27.3)	2 (18.2)	2 (18.2)	1 (9.1)
Often	3 (27.3)	0 (0.0)	1 (9.1)	0 (0.0)
Always	5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)
Impact of pruritus on others, n (%)				
Never	2 (18.2)	9 (81.8)	7 (63.6)	8 (72.7)
Rarely	0 (0.0)	2 (18.2)	2 (18.2)	2 (18.2)
Sometimes	1 (9.1)	0 (0.0)	2 (18.2)	1 (9.1)
Often	5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)
Always	3 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)
Impact of pruritus on sleep, n (%)				
Never	0 (0.0)	7 (63.6)	8 (72.7)	7 (63.6)
Rarely	1 (9.1)	4 (36.4)	1 (9.1)	3 (27.3)
Sometimes	1 (9.1)	0 (0.0)	2 (18.2)	1 (9.1)
Often	5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)
Always	4 (36.4)	0 (0.0)	0 (0.0)	0 (0.0)
Impact of pruritus on mood, n (%)				
Never	0 (0.0)	8 (72.7)	7 (63.6)	9 (81.8)
Rarely	2 (18.2)	3 (27.3)	2 (18.2)	1 (9.1)
Sometimes	1 (9.1)	0 (0.0)	2 (18.2)	1 (9.1)
Often	6 (54.5)	0 (0.0)	0 (0.0)	0 (0.0)
Always	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)
Difficulty sleeping. Yes, n (%)	11 (100)	6 (54.5)	1 (9.1)	2 (18.2)
VAS difficulty sleeping, median (range)	8 (10-1)	1 (7-0)	0 (1-0)	0 (3-0)

SD: Standard deviation; VAS: Visual analogue scale; BMI: Body m ass index; SCORAD: Scoring Atopic Dermatitis.

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Table 2. Descriptive variables of quality of life at baseline visits, 16, 40 and 52 weeks.

Variable		Baseline	Week 16	Week 40	Week 52
HADS, anxiety, mean (SD)		9.2 (3.0)	3.9 (3.4)	3.4 (3.5)	2.6 (2.8)
HADS, depression, mean (SD)		4.7 (3.4)	1.9 (2.5)	2.0 (2.3)	0.6 (1.0)
HADS, total, mean (SD)		13.9 (5.5)	5.8 (5.0)	5.4 (5.0)	3.2 (3.9)
DLQI, mean (SD)		13.9 (8.3)	2.0 (1.8)	1.3 (1.4)	2.1 (2.7)
EQ5D3L mobility problems, n (%)					
	None	11 (100)	11 (100)	11 (100)	11 (100)
	Some	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Many	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EQ5D3L personal care problems, n (%)					
	None	9 (81.8)	11 (100)	11 (100)	11 (100)
	Some	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Many	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EQ5D3L problems in daily activities, n (%)					
	None	6 (54.5)	11 (100)	100 (0.0)	11 (100)
	Some	5 (45.4)	0 (0.0)	0 (0.0)	0 (0.0)
	Many	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EQ5D3L disconfort, pain problems, n (%)					
	None	3 (27.3)	10 (90.1)	10 (90.9)	11 (100)
	Some	8 (72.7)	1 (9.1)	1 (9.1)	0 (0.0)
	Many	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EQ5D3L anxiety/depression problems, n (%)					
	None	3 (27.3)	9 (81.8)	9 (81.8)	11 (100)
	Some	6 (54.5)	1 (9.1)	2 (18.2)	0 (0.0)
	Many	2 (18.2)	1 (9,1)	0 (0.0)	0 (0.0)
EQ5D3L VAS, mean (range)		57 (99-30)	80 (95-50)	84 (99-70)	89 (92-60)

DLQI: Dermatology Life Quality Index; SD: Standard Deviation; EQ5D3L: EuroQol 5 Dimensions; VAS: Visual Analogue Scale; HADS: Hospital Anxiety and Depression Scale.

Table 3. Descriptive of security variables at baseline visits, 16, 40 and 52 weeks.

Variable		Baseline	Week 16	Week 40	Week 52
SBP, mmHg, mean (SD)		127.3 (16.4)	121.8 (14.2)	121.2 (9.7)	128.0 (11.1)
DBP, mmHg, mean (SD)		82.1 (12.4)	78.7 (12.6)	80.0 (10.6)	83.1 (8.4)
Pulse, BPM, mean (SD)		79.0 (17.9)	72.7 (12.6)	76.2 (10.6)	83.7 (7.7)
Temperature, mean Cº (SD)		36.1 (10.3)	36.0 (0.3)	36.2 (0.3)	36.1 (0.3)
Local reaction. Yes, n (%)		2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)
Severity, n (%)					
	Mild	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General reaction. Yes, n (%)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Analytical alteration Yes, n (%)		0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)

SD: Standard Deviation; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; BPM: Beats per minute.

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Table 4. Median value of e VAS of satisfaction with current and previous treatment.

Variable	Dupilumab			Previous
	Week-16	Week-40	Week-52	
Satisfaction with training received to administer treatment, median (range)	9 (10-6)	9 (10-6)	9 (10-6)	6 (10-0)
Satisfaction with information from dermatologist, median (range)	9 (10-6)	9 (10-6)	9 (10-6)	6 (9-0)
Satisfaction with disease control, median (range)	9 (10-6)	9 (10-6)	9 (10-6)	3 (8-0)
Satisfaction with frequency of administration, median (range)	9 (10-6)	9 (10-6)	9 (10-6)	2 (9-0)
Effectiveness of treatment to prolong time between flares, median (range)	9 (10-6)	9 (10-6)	9 (10-6)	2 (9-0)
Effectiveness of treatment in control of flares, Median (range)	9 (10-6)	9 (10-6)	9 (10-6)	2 (8-0)
Overall satisfaction, median (range)	9 (10-8)	9 (10-8)	9 (10-8)	4 (10-0)

VAS: Visual Analog Scale.

Table 5. Comparative analysis of disease severity and symptoms at baseline visits, 16, 40 and 52 weeks.

Variable	Baseline	Week 16	Week 40	Week 52	P value
Weight, mean (SD)	74.7 (14.2)	74.0 (15.3)	75.4 (13.6)	75.0 (15.8)	0.993£
BMI, mean (SD)	27.0 (4.4)	26.8 (4.9)	27.2 (4.2)	27.1 (5.0)	0.994£
SCORAD, mean (SD)	64.5 (19.6)	5.5 (5.9)	5.8 (5.7)	5.3 (6.0)	<0.001£ <0.001Ω (baseline vs. rest)
VAS pruritus, median (range)	8 (10-6)	1 (6-0)	1 (4-0)	1 (6-0)	<0.001¥ 0.003§ (baseline vs. rest) 0.259§ (week 40 vs. week 52)
VAS difficulty sleeping, median (range)	8 (10-1)	1 (7-0)	0 (1-0)	0 (3-0)	<0.001¥ 0.006§ (baseline vs. rest) 0.036§ (week 16 vs. rest)

£: Repeated measures ANOVA; ¥: Friedman Test; Ω: Baseline Student´s T test versus the other visits; § Wilcoxon Test.
SD: Standard deviation; VAS: Visual Analogue Scale; MBI: Body Mass Index.

Figure 1. SCORAD evolution.

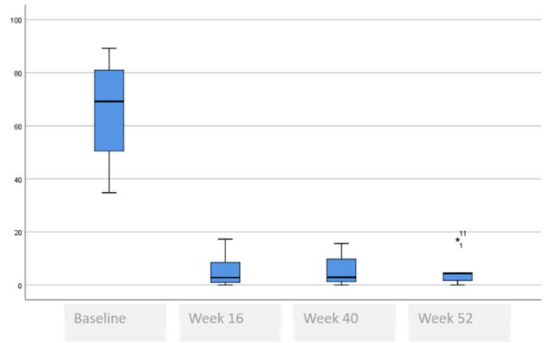

Figure 2. Evolution of itch assessment.

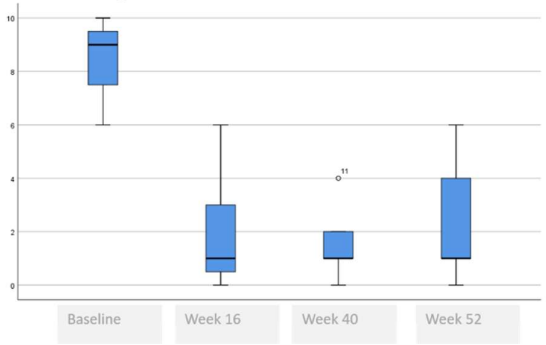

Figure 3. Evolution of difficulty sleeping.

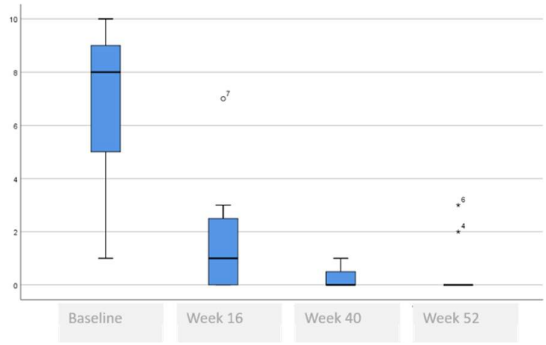

Figure 4. Evolution of the HADS anxiety score.

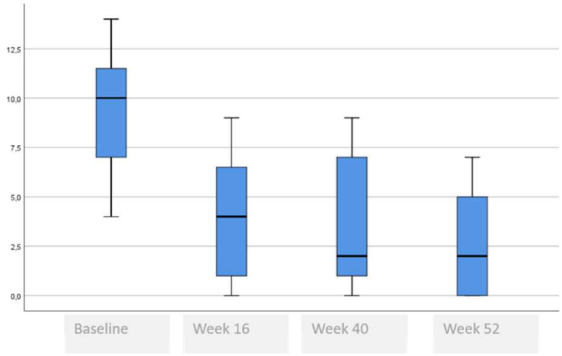

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Table 6. Comparative analysis of quality of life a result perceived by patients at baseline visits, 16, 40 and 52 weeks.

Variable	Baseline	Week 16	Week 40	Week 52	P value
HADS anxiety, mean (SD)	9.2 (3.0)	3.9 (3.4)	3.4 (3.5)	2.6 (2.8)	<0.001£ <0.007Ω (baseline vs. Week 16) <0.224Ω (baseline vs. Week 52)
HADS depression, mean (SD)	4.7 (3.4)	1.9 (2.5)	2.0 (2.3)	0.6 (1.0)	0.001£ <0.008Ω. (baseline vs. Week 16) <0.127Ω. (baseline vs. Week 52)
HADS Total, mean (SD)	13.9 (5.5)	5.8 (5.0)	5.4 (5.0)	3.2 (3.9)	0.001£ <0.004Ω (baseline vs. week 16) <0.138Ω (baseline vs. week 52)
DLQI, mean (SD)	13.9 (8.3)	2.0 (1.8)	1.3 (1.4)	2.1 (2.7)	<0.001£ 0.001Ω (baseline vs. week 52) 0.931 Ω (week 16 vs. week 52)
VAS EQ5D3L, median (range)	57 (99-30)	80 (95-50)	84 (99-70)	89 (92-60)	<0.001£ 0.035 Ω (baseline vs. week 16) 0.225 Ω (week 16 vs. week 52)

£: Repeated measures ANOVA; Ω: Student´s T test; DLQI: Dermatology Life Quality Index; SD: Standard Deviation; EQ5D3L: EuroQol 5D3L; VAS: Visual Analog Scale; HADS: Hospital Anxiety and Depression Scale.

Figure 5. Evolution of the HADS depression score.

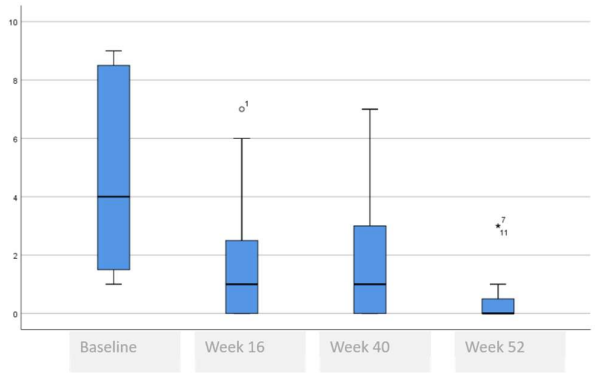

Figure 6 Evolution of the total HADS score.

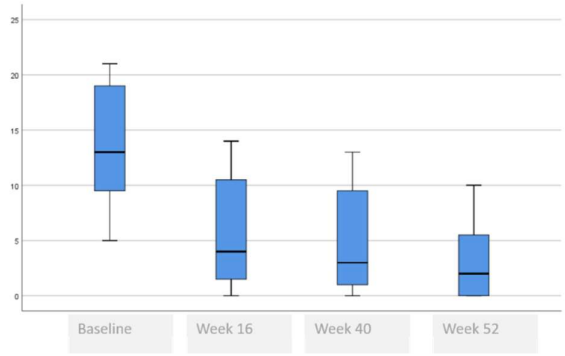

Figure 7. DLQI score evolution.

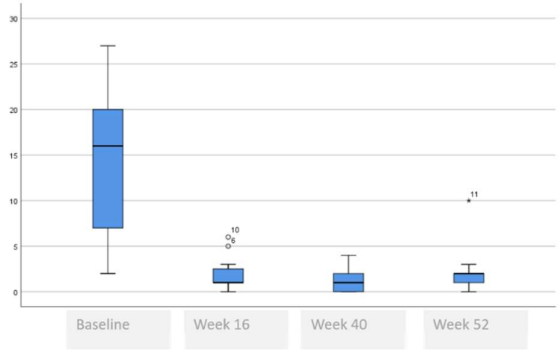

Figure 8. Evolution of the EQ-5D3L

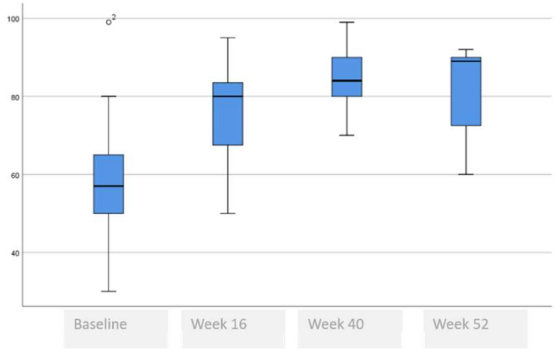

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Table 7. Safety variables

Variable	Baseline	Week 16	Week 40	Week 52	P value
SBP, mmHg, mean (SD)	127.3 (16.4)	121.8 (14.2)	121.2 (9.7)	128.0 (11.1)	0.106£
DBP, mmHg, mean (SD)	82.1 (12.4)	78.7 (12.6)	80.0 (10.6)	83.1 (8.4)	0.689£
Pulse, BPM, mean (SD)	79.0 (17.9)	72.7 (12.6)	76.2 (10.6)	83.7 (7.7)	0.137£
Temperature, mean Cº (SD)	36.1 (0.3)	36.0 (0.3)	36.2 (0.3)	36.1 (0.3)	0.465£

£: Repeated measures ANOVA; SD: Standard Deviation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BPM: Beats er minute.

Table 8. Comparative of satisfaction between Dupilumab and previous treatment measure with VAS.

Variable	Previous	Current at Week 16	P value (previous vs. current at week 16)	Current at week 40	P value (current vs. previous at week 16 and 40)	Current at week 52	P value (previous vs. current at week 40 and 52)
Satisfaction with training received to administer treatment, median (range)	6 (10-0)	9 (10-6)	0.019§	9 (10-8)	0.296§	9 (10-8)	0.811§
Satisfaction with information from dermatologist, median (range)	6 (9-0)	9 (10-6)	0.01§	9 (10-8)	0.397§	9 (10-8)	0.900§
Satisfaction with disease control, median (range)	3 (8-0)	9 (10-6)	<0.001§	9 (10-8)	0.140§	9 (10-7)	0.796§
Satisfaction with frequency of administration, median (range)	2 (9-0)	9 (10-6)	0.001§	9 (10-7)	0.395§	9 (10-7)	0.147§
Effectiveness of treatment to prolong time between flares, median (range)	2 (9-0)	9 (10-6)	<0.001§	9 (10-6)	0.733§	9 (10-5)	0.362§
Effectiveness of treatment in control of flares, Median (range)	2 (8-0)	9 (10-6)	<0.001§	9 (10-4)	0.887§	9 (10-7)	0.104§
Overall satisfaction, median (range)	4 (10-0)	9 (10-8)	0.001§	9 (10-7)	0.640§	9 (10-4)	<0.001§

§: Student´s T of related data

Table 9. Evolution of the CRES-4 score.

Variable	Week 16	Week 40	Week 52	P value
Satisfaction, mean (SD)	90.9 (24.2)	92.7 (13.4)	83.6 (19.6)	0.079∞
Problem solution, mean (SD)	100 (0.0))	96.3 (8.0)	100 (0.0)	0.135∞
Perception of emotional change, mean (SD)	67.1 (19.4)	71.5 (12.6)	69.3 (10.2)	0.690∞

∞: Friedman´s test; SD: Standard Deviation.

4. Discussion

The results of this study show that dupilumab 300 mg. q2w in monotherapy promotes a rapid and sustained statistically significant improvement in de SCORAD score in adults with moderate to severe atopic dermatitis at week 16 and is maintained until week 52. The improvement in the SCORAD score is comparable with previous studies performed: the 2017 SOLO-1 and SOLO-2 studies [16] al week 16; the 2018 phase

III LIBERTY AD CAFÉ trial [26] where dupilumab every two weeks reduced the SCORAD index by 62.4%, compared with 91% in our study; the 52- week LIBERTY AD CHRONOS study had a cut-off point at 16 weeks, with which our results may be compared [27]. At week 16, there was a significant reduction in the SCORAD index of 62.1%. In a polled analysis of a phase 2a and a phase 2b study and a sub analysis of the 2b study [28] also show a significantly improvement of SCORAD al week 12. In a real-life multicenter study [29], a 3 months follow-up shows a significative reduction of the SCORAD score, and in a post hoc analysis Barbarot, et al. [30] included 2,444 patients in four placebo-controlled, double-blind, randomized, phase 3 trials. SOLO 1 and SOLO 2 evaluated 16 weeks of dupilumab monotherapy against placebo. CAFÉ and CHRONOS evaluated dupilumab with concomitant topical corticosteroids (TCS) against TCS alone for 16 and 52 weeks, respectively and published SCORAD score show significative reduction at both week 16 and week 56 respectively, similar to our results. Tofte et al. [28] report a significant and rapid improvement of pruritus reduction in the first week and it continues to decrease its intensity until week 12, data similar to that observed in our sample in week 4, which are maintained until week 52. Similarly, de Bruin-Weller, et al. (26) document a reduction in pruritus, measured as the percentage of patients achieving reductions of >4 points on the NRS scale, compared with a reduction of 7 points in the VAS for itching found in our study ($p=0.003$) at week 16. Also, Blauvelt, et al. (27) evaluated itching as a secondary outcome, obtaining significant reductions, in a similar way to those obtained by us. And Simpson, et al. (16) show an improvement in pruritus symptom y the SOLO-1 and SOLO-2 studies. These results cannot be compared with ours but they do support our findings. In addition to its positive effect on itch, improvement in sleep was observed in patients treated with dupilumab, with a reduction in the VAS difficulty-in-sleeping scale of 8 to 1 ($p=0.006$) and disappearing at week 40 and week 52 ($p<0.001$), similar to the results reported by Simpson et al. in 2016 [15] who measured improvements by a VAS (reduction of 3.7) and the POEM questionnaire. Tofte, et al. [28] observed in a pooled analysis of two phase 2 clinical trials a rapid and significant reduction (week 2) in sleep disturbance that was maintained until week 12 ($p<0.05$ vs. placebo). The 52- week LIBERTY AD CHRONOS study had a cut-off point at 16 weeks, with which our results may be compared [27]. At week 16 there was a significant reduction in the DLQI of 9.7 points, and in the HADS of 4.9 which, as previously mentioned, is consistent with previously-published results. In the 2018 phase III LIBERTY AD CAFÉ trial [26], dupilumab every two weeks reported a mean reduction of 6.1 in the HADS index, in line with the 5.8 reduction in our study at week 16, and a reduction of 9.5 in the DLQI score [28], similar to the 11.9 reduction in our study. Tofte, et al. [28], also report mild or moderate adverse effects, similar to those obtained by us, except for conjunctivitis. In the two clinical trials, they report 9.3% and 1.7% respectively, very divergent data between one and the other, which differ from our data in which we did not observe conjunctivitis probably due to our precaution in the use of artificial tears at the beginning of the treatment and maintaining it throughout.

We also analyzed satisfaction with treatment, measured using the validated CRES-4 scale [25]. The results show good satisfaction with treatment, both clinically and in communication with physician, and the emotional perception of the treatment. The perception of satisfaction was also assessed with a series of "ad hoc" questions made using VAS, among which the score of 4 out to 10 in relation to previous treatments ant of 9 out to 10 with dupilumab stand out, both in week 16, such us at week 40 and week 52 (<0.001). This is an important contribution of the present study, as this factor has not been previously reported.

Our study had some limitations. It was a single-center study carried out in a small number of patients. The strengths of the study are the extensive data collection and control to guarantee quality, and the assessment of patient's satisfaction with the treatment.

5. Conclusions

In our study we have observed in week 52 that dupilumab is effective in the treatment of adult patients with moderate to severe AD, rapidly reducing the signs and symptoms of AD and improving psychological impact and quality of life. The safety profile was excellent and we have not had cases of conjunctivitis, probably due to the preventive use of artificial tears during treatment, whose use we recommend. Adherence to treatment and perception of satisfaction show that patients value dupilumab treatment significantly better compared to previous treatments.

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Institutional Review Board Statement: The study was conducted according to the guidelines of Declaration of Helsinki, and authorized by the Spanish Agency for Medicines and Health Products (AEMPS). The project identification code is NPP 14985 (015649). Date of approval: October 2017, by the AEMPS.

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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