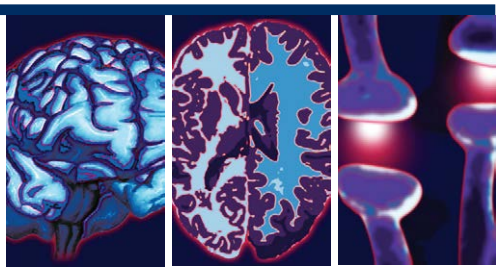

Adult Patients with Atopic Dermatitis Treated with Dupilumab in Routine Clinical Practice: Preliminary Data at Week 16

Servando E. Marron[1,2,†], Lucia Tomas-Aragones[3,2], Carlos A. Moncin-Torres[4], Manuel Gomez-Barrera[5], Víctor M. Alcalde-Herrero[1,2], Francisco Javier Garcia-Latasa de Aranibar[1,2]

ABSTRACT

Introduction

Atopic dermatitis is a chronic inflammatory skin disease characterized by intense pruritus. Dupilumab is a human monoclonal antibody specifically targeted to block the interleukin-4 alpha receptor (IL-4), inhibiting signalling for interleukin-4 and interleukin-13 in the treatment of atopic dermatitis.

Material and Method

Longitudinal study performed under routine clinical practice in the dermatology department of the Royo Villanova Hospital. Eleven adult patients with moderate-severe AD are being treated in a program of extended use of medication authorized by the Spanish Agency of Medicines and Health Products (AEMS). Patients are treated with dupilumab 300 mg subcutaneous injection every 2 weeks with an initial loading dose of 600 mg. artificial tears are recommended for the preventive management of conjunctivitis, and emollient creams for the skin.

Results

Week 16 analysis shows a reduction in pruritus ($p=0.003$) and in the severity of the disease (91% reduction, $p<0.001$). Quality of life scores, measured with the DLQI are improved (from 13.9 to 2.0, $p=0.001$) as with the health thermometer of the EQ-5D (from 57 to 80, $p=0.035$). Patients do not report conjunctivitis.

Conclusions

The use of dupilumab in routine clinical practice proves to be effective and safe, with an improvement of psychosocial impact and quality of life. Its safety profile is excellent, as well as adherence to treatment and patient satisfaction.

Keywords

Atopic dermatitis, Dupilumab, Treatment outcome, Safety management, Adherence to treatment, Patient satisfaction, Patient reported outcomes

[1]Dermatology Department, Royo Villanova Hospital, Zaragoza, Spain

[2]Aragon Psychodermatology Research Group (GAI+PD), Zaragoza, Spain

[3]Psychology Department, University of Zaragoza, Zaragoza, Spain

[4]Pharmacy Department, Royo Villanova Hospital, Zaragoza, Spain

[5]San Jorge University, Zaragoza, Pharmacoeconomics & Outcomes Research Iberia (PORIB), Spain

[†]Author for correspondences: Servando E. Marron, Dermatology Department, Royo Villanova Hospital, Avda. San Gregorio, 30, 50015 Zaragoza, Spain, Tel: +34 608032227; email: semarron@aedv.es

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, 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 signalling 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. Currently, the reimbursement price in Spain is pending.

The objective of this ongoing study is to evaluate the efficacy, safety, psychosocial impact, quality of life, adherence to treatment and satisfaction in adult patients with AD treated with subcutaneous dupilumab for one year in routine clinical practice. A data analysis was made at week 16 and we present the preliminary results here. Definitive data will be presented at week 52.

Material and Method

Study design and participants

We are carrying out a one-year prospective study in the dermatology department of the Royo Villanova Hospital, Zaragoza, Spain. We included 11 adult patients with moderate-to-severe AD who had not responded satisfactorily to previous treatment (topical and systemic).

The study was carried out according to the provisions of the Helsinki Declaration and current Spanish legislation. Treatment with dupilumab was possible through adherence to a program of extended medication use authorized by the Spanish Agency for Medicines and Health Products (AEMPS).

All patients were evaluated and authorized individually by AEMPS, and the authorization must be renewed every 12 weeks for treatment to continue.

All patients gave written signed informed consent to be included in the program and authorized the use of the clinical data obtained.

Patient inclusion

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. The period available for the request to include patients was two months.

Procedure

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: selection, treatment initiation (baseline), weeks 4, 8, 12, 16 and then every 12 weeks (weeks 28, 40 and 52).

A specific questionnaire was prepared for each treatment visit to guarantee data quality.

Study variables

The sociodemographic variables collected were: age, sex, educational level, cohabitation, and occupational status, stressors during the previous 6 months, height, weight and the body mass index (BMI).

Clinical variables collected were: age at onset of AD, years of evolution, patient-perceived severity in the last year and currently, and topical and systemic treatments administered.

Outcome variables: a) AD severity using the Scoring Atopic Dermatitis (SCORAD) index [18], b) variables related to pruritus (stinging, burning or pain) and its negative consequences (relationships, sleep disturbance, mood and difficulty sleeping), c) anxiety and/or depressive symptoms using the Hospital Anxiety and Depression Scale (HADS) [19], d) quality of life using the EuroQol 5D-3L (EQ-5D-3L) [20] and Dermatology Life Quality Index (DLQI) [21], e) patient satisfaction using an ad hoc visual analogue scale (VAS) [22] and the Consumer Reports Effectiveness Scale (CRES-4) [23], which measures satisfaction with treatment, f) treatment adherence, checked by counting boxes and syringes consumed at each visit, g) safety, and h) adverse effects.

■ 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 variables and the median and range were calculated. Comparisons were made with the Chi square test for qualitative variables and the Student T test for related data when the variable was distributed normally and the Wilcoxon T 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. The data were analysed using SPSS 21.0.

Results

Between November 14, 2017 and January 16, 2018, authorization was requested to include 11 patients with AD in the programme of treatment with subcutaneous dupilumab every 2 weeks.

The time from the request to the availability of the medication to start treatment was 20-54 days with a mean of 32 days.

■ Patient description at selection

Patients' demographic and clinical results at the selection visit are shown in **Table 1**.

■ Comparative efficacy and safety analysis, baseline visit-week 16

Comparison of the results at baseline and week 16 shows that itching symptoms were reduced from 8 to 1 (p=0.003) and disease severity (SCORAD index) from 64.5 to 5.5 (reduction of 91, p<0.001) at week 16 **(Table 2)**.The HADS score fell by 9.2 to 3.9 (p=0.007) for anxiety and from 4.7 to 1.9 (p=0.008) for depression. There was a reduction from 13.9 to 2.0 (p=0.001) in the DLQI questionnaire and from 57 to 80 (p=0.035) in the EQ-5D VAS **(Table 3)**. No relevant safety effects were found **(Table 4)**.

■ Satisfaction with treatment

Comparison of satisfaction with treatment at week 16 and previous treatment shows satisfaction improved with current treatment with dupilumab in all items analysed **(Table 5)**.

Table 1: Patient characteristics at the selection visit

Variable	
Sex, n (%)	
Female	9 (81.8)
Male	2 (18.2)
Educational level, n (%)	
Secondary	6 (54.5)
Higher	5 (45.5)
Cohabitation, n (%)	
Family	8 (72.7)
Alone	3 (27.3)
Occupational situation, n (%)	
Students	3 (27.3)
Active workers	5 (45.5)
Retired	1 (9.1)
Unemployed	1 (9.1)
Sick leave	1 (9.1)
Stressful life events, n (%)	5 (45.5)
Age in years, mean (± SD)	33.2 ± 15.6
Weight in kg, mean (± SD)	72.0 ± 14.4
Height in cm, mean (± SD)	165.9 ± 5.6
BMI in kg/m^2, mean (± SD)	36.1 ± 4.5
Years of illness, mean (± SD)	16.6 ± 22.5
Years of evolution, mean (± SD)	17.7 ± 12.8
SCORAD, mean (± SD)	61.7 ± 15.5
Self-perception of disease, n (%)	
Serious	10 (90.9)
Moderate	1 (9.1)
Mild	0 (0.0)
Topical treatments, n (%):	
Corticosteroids	11 (100)
Emollients	11 (100)
Fusidic acid	11 (100)
Tacrolimus	8 (72.7)
Fusidic acid + betamethasone	3 (27.3)
Pimecrolimus	2 (18.2)
Mupirocin	2 (18.2)
Systemic treatments, n (%):	
Prednisone	10 (90.9)
Cyclosporine	5 (45.5)
Phototherapy	2 (18.2)
Methotrexate	2 (18.2)
Apremilast	1 (9.1)
Dexchlorpheniramine/betamethasone	1 (9.1)
Hydroxyzine	1 (9.1)
Bilastine	6 (54.5)
Omeprazole	1 (9.1)

ABB: SD: Standard deviation; SCORAD: Scoring Atopic Dermatitis.

Table 2: Symptoms at baseline and 16 weeks.

Variable	Baseline	Week 16	Value p
Severity, n (%)			
Without lesions	0 (0.0)	3 (27.3)	
Almost no lesions	0 (0.0)	2 (18.2)	NC
Mild	0 (0.0)	4 (36.4)	
Moderate	0 (0.0)	2 (18.2)	
Severe	11 (100)	0 (0.0)	
Weight, mean (SD)	74.7 (14.2)	74.0 (15.3)	£0.623
BMI, mean (SD)	27.0 (4.4)	26.8 (4.9)	£0.636
SCORAD, mean (SD)	64.5 (19.6)	5.5 (5.95)	<0.001£
Itching. Yes, n (%)	11 (100)	8 (72.7)	NC
VAS pruritus, mean (range)	8 (10-6)	1 (6-0)	0.003¥
Pruritus, characteristics. Yes, n (%)			
Itching only	4 (36.4)	9 (81.8)	0.618Ω
Burning	8 (72.7)	0 (0)	NC
Stinging	8 (72.7)	0 (0)	NC
Pain	7 (63.6)	0 (0)	NC
Pruritus, frequency. Yes, n (%)			
Never	0 (0.0)	2 (18.2)	
Rarely	0 (0.0)	3 (27.3)	0.618Ω
Sometimes	1 (9.1)	4 (36.4)	
Often	5 (45.5)	2 (18.2)	
Always	5 (45.5)	0 (0.0)	
Life-threatening itching, n (%)			
Never	0 (0.0)	6 (54.5)	
Rarely	0 (0.0)	3 (27.3)	NC
Sometimes	3 (27.3)	2 (18.2)	
Often	3 (27.3)	0 (0.0)	
Always	5 (45.5)	0 (0.0)	
Impact of pruritus on others, n (%)			
Never	2 (18.2)	9 (81.8)	
Rarely	0 (0.0)	2 (18.2)	NC
Sometimes	1 (9.1)	0 (0.0)	
Often	5 (45.5)	0 (0.0)	
Always	3 (27.3)	0 (0.0)	
Impact of pruritus on sleep, n (%)			
Never	0 (0.0)	7 (63.6)	
Rarely	1 (9.1)	4 (36.4)	NC
Sometimes	1 (9.1)	0 (0.0)	
Often	5 (45.5)	0 (0.0)	
Always	4 (36.4)	0 (0.0)	
Impact of pruritus on mood, n (%)			
Never	0 (0.0)	8 (72.7)	
Rarely	2 (18.2)	3 (27.3)	NC
Sometimes	1 (9.1)	0 (0.0)	
Often	6 (54.5)	0 (0.0)	
Always	2 (18.2)	0 (0.0)	
Difficulty sleeping. Yes, n (%)	11 (100)	6 (54.5)	NC
VAS difficulty sleeping, medium (range)	8 (10-1)	1 (7-0)	0.006¥

ABB: NC: Not calculable as did not meet requirements of chi-square test; £: Student t test for related data;

¥: Wilcoxon test; Ω: Fisher's exact test

SD: Standard deviation; VAS: Visual Analogue Scale; BMI: Body mass index. SCORAD: Scoring Atopic Dermatitis.

Table 3: Self-perceived quality of life and results at baseline and week 16.

Variable	Basal	Week 16	P value
HADS anxiety, mean (SD)	9.2 (3.0)	3.9 (3.4)	£0.007
HADS depression, mean (SD)	4.7 (3.4)	1.9 (2.5)	£0.008
Total, mean HADS (SD)	13.9 (5.5)	5.8 (5.0)	£0.004
DLQI, mean (SD)	13.9 (8.3)	2.0 (1.86)	£0.001
EQ5D mobility problems, n (%) None Some Many	 11 (100) 0 (0.0) 0 (0.0)	 11 (100) 0 (0.0) 0 (0.0)	NC
EQ5D personal care problems, n (%) None Some Many	 9 (81.8) 2 (18.2) 0 (0.0)	 11 (100) 0 (0.0) 0 (0.0)	NC
EQ5D problems in daily activities, n (%) None Some Many	 6 (54.5) 5 (45.4) 0 (0.0)	 11 (100) 0 (0.0) 0 (0.0)	NC
EQ5D discomfort, pain problems, n (%) None Some Many	 3 (27.3) 8 (72.7) 0 (0.0)	 10 (90.9) 1 (9.1) 0 (0.0)	NC
EQ5D anxiety/depression problems, n (%) None Some Many	 3 (27.3) 6 (54.5) 2 (18.2)	 9 (81.8) 1 (9.1) 1 (9.1)	NC
EQ5D VAS, mean (range)	57 (99-30)	80 (95-50)	£0.035

ABB: £: Student t test for related data

DLQI: Dermatology Quality of Life Index; SD: Standard deviation; EQ5D: EuroQol 5 Dimensions; VAS: Visual Analogue Scale; HADS: Hospital Anxiety and Depression Scale; NC: Not calculable

Table 4: Safety variables at baseline and week 16.

Variable	Baseline	Week 16	P value
Prior to administration			
SBP, mmHg, mean (SD)	131.6 (10.4)	127.3 (12.5)	£0.226
DBP, mmHg, mean (SD)	81.5 (9.4)	82.5 (8.4)	£0.488
Pulse, BPM, mean (SD)	79.8 (9.4)	75.8 (12.4)	£0.148
Temperature, mean Cº (SD)	36.1 (0.36)	36.1 (0.3)	£0.788
After administration			
SBP, mmHg, mean (SD)	127.3 (16.4)	121.8 (14.2)	£0.064
DBP, mmHg, mean (SD)	82.1 (12.4)	78.7 (12.6)	£0.301
Pulse, BPM, mean (SD)	79 (17.9)	72.7 (12.6)	£0.238
Temperature, mean Cº (SD)	36.1 (0.3)	36.0 (0.3)	£0.461
Local reaction. Yes, n (%)	2 (18.2)	0	NC
Severity, n (%) Mild Moderate Severe	 2 (18.2) 0 (0.0) 0 (0.0)	 0 (0.0) 0 (0.0) 0 (0.0)	NC
General reaction. Yes, n (%)	0 (0.0)	0 (0.0)	NC
Training on treatment administration. Yes, n (%)	10 (90.9)	11 (100)	NC
Analytical alterations. Yes, n (%) Mild Moderate Severe	 0 (0.0) 0 (0.0) 0 (0.0)	 1 (9.1) 0 (0.0) 0 (0.0)	NC

ABB: £: Student t test for related data
SD: Standard deviation; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; BPM; Beats per minute; NC: Not calculable.

Table 5: Comparison of satisfaction between current treatment with Dupilumab and previous treatment.			
Variable	**Dupilumab**	**Previous**	**P value**
Overall satisfaction, median (range)	9 (10-8)	4 (10-0)	0.001§
Effectiveness of treatment in the control of flares, median (range)	9 (10-6)	2 (8-0)	<0.001§
Effectiveness of treatment to prolong time between flares, median (range)	9 (10-6)	2 (9-0)	<0.001§
Satisfaction with frequency of administration, median (range)	9 (10-6)	2 (9-0)	0.001§
Satisfaction with disease control, median (range)	9 (10-6)	3 (8-0)	<0.001§
Satisfaction with information from dermatologist, median (range)	9 (10-6)	6 (9-0)	0.01§
Satisfaction with training received to administer treatment, median (range)	9 (10-6)	6 (10-0)	0.019§
ABB: §: Student t test for independent samples			

Discussion

These preliminary results of this study of the efficacy, safety, quality of life and patient-perceived variables in patients with AD treated with dupilumab show that dupilumab was well tolerated and effective in the treatment of adult patients with moderate-to-severe AD [24].

There was an improvement in the quality of life and the psychosocial impact associated with AD, confirming the good results shown in clinical trials versus placebo.

In the 2018 phase III LIBERTY AD CAFÉ trial [25] dupilumab every two weeks reduced the SCORAD index by 62.4%, compared with 91% in our study. The same study reported a mean reduction of 6.1 in the HADS index, in line with the 5.8 reduction in our study, a reduction of 9.5 in the DLQI score, similar to the 11.9 reduction in our study, and 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).

The 52- week LIBERTY AD CHRONOS study had a cut-off point at 16 weeks, with which our results may be compared [26]. The main outcome was the global investigator evaluation scale and secondary outcomes included pruritus and quality of life results. At week 16, there was a significant reduction in the SCORAD index of 62.1%, in the DLQI of 9.7 points, and in the HADS of 4.9, which, as previously mentioned, is consistent with previously-published results.

The 2017 SOLO-1 and SOLO-2 studies [16] found similar results with respect to reductions in disease severity and pruritus and improvements in the quality of life using least-squared means. These results cannot be compared with ours but they do support our findings.

Improvement in sleep was observed, with a reduction in the VAS difficulty-in-sleeping scale of 8 to 1 (p=0.006), 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.

The studies described above also reported a good safety profile without noticeable alterations in the parameters analysed.

We also analysed satisfaction with treatment, measured using the validated CRES-4 scale [23]. The results show good satisfaction with treatment, both clinically and in communication with physician, and the emotional perception of the treatment. This is the main contribution of the present study, as this factor has not been reported hitherto.

Our study had some limitations. It was a single-centre study carried out in a small number of patients. However, as dupilumab is not yet commercially available in Spain, because the reimbursement price has not been fixed, and the study was made using the expanded use programme, the difficulties involved, in addition to patient management, were considerable. The strengths of the study are the extensive data collection and control to guarantee quality, and the first report on satisfaction with treatment.

Conclusions

According to the preliminary data at week 16, dupilumab is effective in the treatment of adult patients with moderate-severe AD, rapidly reducing the clinical signs and symptoms of DA and improving the psychosocial impact and quality of life. The safety profile was excellent and there were no cases of conjunctivitis after preventive use of artificial tears was recommended. Treatment adherence was excellent and patient satisfaction was significantly better than with previous treatments.

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