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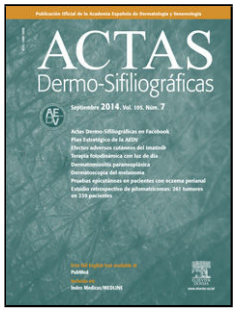

FR-Espaciamiento de la dosis de dupilumab en dermatitis atópica: ¿optimización o fracaso terapéutico?

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FORO DE RESIDENTES

FR-Espaciamiento de la dosis de dupilumab en dermatitis atópica: ¿optimización o fracaso terapéutico?

[[Translated article]]RF-Longer Dupilumab Dosing Intervals in Atopic Dermatitis: Optimization or Therapeutic Failure?

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Palabras clave: Dupilumab; Dermatitis atópica; Reducción dosis; Optimización terapéutica; Adulto; Eficiencia

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Dupilumab is a human IgG4 monoclonal antibody that targets the interleukin 4 receptor alpha (IL-4Rα), which inhibits IL-4 and IL-13. It has been approved to treat moderate-to-severe atopic dermatitis (AD), moderate-to-severe asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis. Regarding AD, the regimen for adults is a loading dose of 600 mg, followed by 300 mg every 2 weeks (Q2W).

The therapeutic optimization of biological drugs consists of down-titration in patients with a sustained good response, without loss of efficacy. This practice is rooted in psoriasis and some rheumatologic diseases to avoid unnecessary overtreatment, reduce side effects, and improve economic efficiency[1,2].

Below we'll be discussing the results of 5 studies of patients with well-controlled AD on dupilumab, in whom the dosing interval was extended beyond the above-mentioned 2-week threshold.

The first study to explore this idea was the randomized LIBERTY AD SOLO-CONTINUE clinical trial, which is a continuation of the trials that led to the approval of dupilumab for the management of AD. It studied a total of 422 patients categorized into 4 groups based on the dosing interval: Q1W/Q2W, Q4W, and Q8W. Thirty-six weeks after down-titration, no significant differences were reported in the percentage change observed in the Eczema Area and Severity Index (EASI), or in the proportion of patients with Investigator Global Assessment (IGA) 0-1 between the Q1W/Q2W and Q4W groups. Conversely, a proportion of patients with EASI-75 was lost ($p = 0.045$), and the number of patients with, at least, a 3-point increase in the pruritus numeric rating scale (P-NRS) ($p = 0.02$) increased. The Q8W group significantly reduced efficacy in the above-mentioned scales[3].

Afterwards, a Dutch cohort of 90 patients compared the EASI of the Q2W regimen vs the Q4W and Q6W/Q8W regimens. Down-titration was gradual, first to Q3W, and then for those who maintained responses doses were further spaced out. After an, at least, 6-month follow-up, no significant EASI increases were seen in either Q4W or Q6W/Q8W. While the P-NRS remained stable in the Q4W group, it increased in the Q6W/Q8W group ($p = 0.01$). Despite the reduced drug levels, the severity biomarkers PARC/CCL18 and TARC/CCL17 remained low[1].

A French series of 88 patients identified 3 predictors of sustained response after dose reduction: spacing due to good sustained response rather than side effects ($p = 0.034$), older age ($p = 0.006$), and lower monthly dose of topical corticosteroids (0.016). Data from the reviewed studies are summarized in table 1[4].

In conclusion, various authors propose a consensual and gradual down-titration of dupilumab in well-controlled patients. It has been hypothesized that the sustained response is due to the selection of super responders, in whom a lower drug level saturates the pharmacological target[1,2,4,5]. Conducting controlled studies aims to avoid iatrogenesis and promote efficiency with the advent of new drugs.

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Table 1. Studies in which the dupilumab dose was spaced out due to sustained good response

Study type	Inclusion criteria	Primary measurement[a]	Regimen	No. of Patients	Element for statistical comparison	Result	References
Randomized clinical trial	> 18 years, 16 weeks Q1W/Q2W DUPI 300, EASI-75 IGA 0-1	% change in EASI No. of patients with EASI-75 after 36 weeks	Q1/2W Q4W Q8W Placebo	169 86 84 83 n = 442	%EASI-0.06, EASI-75 71, 6% %EASI and EASI-75 of the Q1/2W regimen	%EASI-0.06, EASI-75 71.6% vs %EASI-0.06, EASI-75 71.6%, %EASI-3.84 (NS), EASI-75 58.3% (p = 0.04), %EASI-6.84 (p = 0.02), EASI-75 54.9% (p = 0.01), %EASI-21.6 (p < 0.001), EASI-75 30.4% (p < 0.001)	3
Prospective cohort	>18 years, 52 weeks Q2W with DUPI 300, EASI < 7 for 6 months	EASI and P-NRS after 6 months	Q2W Q4W Q8W	30 30 30 n = 90	EASI 6.4, P-NRS 4.0 vs EASI 1.7, P-NRS 2.0, EASI 2.3, P-NRS 2.0 EASI and P-NRS reached by every group before down-titration	EASI 5.4 (NS), P-NRS 4.0 (NS), EASI 1.5 (NS), P-NRS 2.0 (NS), EASI 2.9 (NS), P-NRS 3.0 (p < 0.01)	1
Case series	>18 years, SCORAD50, down-titration	Response persistence (unspecified scale) after 6.3 months	Q2W Q4W	N = 55[b]	Data not provided in the original article	At the 6.3-month follow-up, 35 individuals maintained/increased spacing. Data not provided by the lead author	4
Case series	>18 years, 52 weeks Q2W with DUPI 300, EASI≤ 7 and DLQI≤ 5 for 6 months	EASI, P-NRS, DLQI after 32 weeks	Q3W Q4W	35 9 n = 44[b]	EASI 0.39, P-NRS 1.04, DLQI 3.28 vs EASI 0.18, P-NRS 1.05, DLQI 3.55 EASI, P-NRS and DLQI reached by every group before down-titration	EASI 0.45 (NS), P-NRS 0.94 (NS), DLQI 3.2 (NS), EASI 0.22 (NS), P-NRS 1.14 (NS), DLQI 2.8 (NS)	2
Case series	>18 years, 52 weeks Q2W with DUPI 300, IGA 0-1	EASI and IGA after 12 months	Q3W Q4W Q2W[c]	n = 17	IGA 1.00, EASI - 16.05 IGA and EASI reached by every group before down-titration	IGA 1.42 (NS), EASI-20,10 (NS) Data not broken down by groups	5

All significant changes were due to loss of efficacy in some scale.

[a] When multiple measurements were available, the most recent one was used, except in [4] where only the described data was available.

[b] Patients who increased the dose interval due to side effects were not included in this table.

[c] Dose was down-titrated to 200 mg of dupilumab every 2 weeks.

DLQI, Dermatology Life Quality Index; DUPI, dupilumab; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NS, not significant; P-NRS, Pruritus Numeric Rating scale; QXW, every "X" No. of weeks.