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Dupilumab discontinuation in atopic dermatitis. Suspension may be an option? Follow-up of twelve cases

Mirian Casas-Vargas[1]; Cindy Cáceres-Salamanca[2]; María Fernanda Ordóñez-Rubiano[3]

SUMMARY

Background: Dupilumab is the first biologic treatment approved for moderate to severe atopic dermatitis (AD) with excellent safety profile and efficacy, but currently there is little literature about its persistence. **Objective:** Describe the treatment outcomes related to discontinuation of dupilumab in a cohort of patients in Bogotá, Colombia. **Methods:** We conducted a retrospective review of the clinical charts from 101 AD patients who were receiving dupilumab. Eligible cases included patients who suspended treatment, regardless of the reason for discontinuation. **Results:** Discontinuation was identified in 12 patients (11.8%), predominantly due to insurance issues (58.3%), adverse effects (8.3%), pregnancy (8.3%), no need for dupilumab (8.3%), and difficulty accessing medication during the COVID-19 pandemic (8.3%). After dupilumab suspension, without restarting it, 3 (33.3%) patients required immunomodulatory therapy, and 1 (11%) patient phototherapy; the remaining 8 (55%) continued only with topical treatment. **Conclusions:** Our report opens the possibility for more studies about the discontinuation of dupilumab in AD patients who exhibit certain characteristics, such as shorter course of the disease, fewer atopic comorbidities, and less previous use of systemic immune-modulators.

Key Words: Antibodies; Atopic dermatitis; COVID-19; Dupilumab; Humanized; Monoclonal; Therapy.

1. Atopic Dermatitis Clinic, Department of Dermatology, Cayre Clinical Center, Bogotá, Colombia. ORCID: https://orcid.org/0000-0003-0414-3562
2. Foundation for Research in Dermatology - FUNINDERMA, Bogotá, Colombia. ORCID: https://orcid.org/0000-0003-3771-5547
3. Atopic Dermatitis Clinic, Department of Dermatology, Cayre Clinical Center. Division of Dermatology, Military Central Hospital, Bogotá, Colombia. ORCID: https://orcid.org/0000-0002-9802-7978

Correspondencia: Mirian Casas-Vargas; **email:** miriancasasdermatologa@gmail.com

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SUSPENSIÓN DE DUPILUMAB EN DERMATITIS ATÓPICA. ¿ES UNA OPCIÓN LA SUSPENSIÓN? SEGUIMIENTO DE 12 CASOS

RESUMEN

Antecedentes: dupilumab es el primer tratamiento biológico aprobado para la dermatitis atópica (DA) moderada a severa, con un perfil de seguridad y eficacia excelente; sin embargo, hasta el momento hay poca literatura sobre su persistencia. **Objetivo:** describir los resultados del tratamiento relacionados con la suspensión de dupilumab en una cohorte de pacientes en Bogotá, Colombia. **Métodos:** realizamos una revisión retrospectiva de las historias clínicas de 101 pacientes con DA que recibían dupilumab. Los casos elegibles incluyeron pacientes que suspendieron el tratamiento, independientemente de la razón de la suspensión. **Resultados:** se identificó la suspensión en 12 pacientes (11,8%), predominantemente por cuestiones de seguros (58,3%), efectos adversos (8,3%), embarazo (8,3%), no necesitar dupilumab (8,3%) y dificultad de acceso al medicamento durante la pandemia por COVID-19 (8,3%). Después de la suspensión de dupilumab sin reiniciar el tratamiento, tres pacientes (33,3%) requirieron terapia inmunomoduladora y un paciente (11%), fototerapia; los demás continuaron solo con tratamiento tópico (ocho pacientes, 55%). **Conclusiones:** nuestro informe abre la posibilidad de más estudios sobre la suspensión de dupilumab en pacientes con DA que tienen algunas características, como un curso más corto de la enfermedad, menos comorbilidades atópicas y menos uso previo de inmunomoduladores sistémicos.

Palabras Clave: Anticuerpos; COVID-19; Dermatitis atópica; Dupilumab; Humanizados; Monoclonales; Terapia.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a significant impact on patients' quality of life, affecting 20% of children and 2-8% of adults. Indeed, 10% of those affected require systemic treatment [1, 2].

Dupilumab is a fully human IgG4 monoclonal antibody that interferes with the T helper (Th) 2 axis, which is crucial in all AD phenotypes and endotypes, by blocking IL-4 and IL-13 signaling [3, 4]. Dupilumab is approved for children, adolescents, and adult patients with moderate to severe disease who are unresponsive to topical therapy. In practice, it is typically prescribed for individuals who are not candidates for, or who have failed to respond to, phototherapy and systemic immune-modulator therapy (SIMT) [5].

Previously, treatments for moderate-to-severe AD included phototherapy, which was not always available or affordable, and SIMT such as cyclosporine, methotrexate, mycophenolate mofetil, and systemic corticosteroids. However, none of these treatments have demonstrated long-term effectiveness, and safety concerns exist, with some not approved in many countries for AD. Nevertheless, these therapies are still utilized and are considered second-line treatments in various international guidelines. Additionally, the use of biologics may be conditioned by prior exposure to phototherapy or SIMT, possibly because dupilumab, being a long-term and expensive treatment, is reserved for cases where other options have been exhausted [6, 7].

Dupilumab has demonstrated sustained efficacy in reducing signs, symptoms, and improving the quality of life in patients with atopic dermatitis (AD), while maintaining a favorable safety profile, making it suitable for long-term treatment of AD [3]. The long-term effectiveness of dupilumab is closely tied to therapy persistence and adherence; discontinuation of treatment may lead to poorer patient outcomes or increased healthcare costs. However, it's important to note that individual patients may experience varying outcomes [4, 5].

MATERIAL AND METHODS

We conducted a descriptive retrospective study from March 6, 2020 to February 27, 2021, using the clinical charts of 101 AD patients treated with dupilumab 300 mg every other week. This protocol was approved by the Cayre Fracture Risk "Institutional Investigation Board"; since this research is considered low-risk, it was not necessary to obtain informed consent. Nonetheless, adherence to the principles outlined in the Helsinki and Belmont declarations was ensured. Demographics, comorbidities, previous and current treatments, severity of the disease, and other relevant characteristics were recorded. Statistical analysis was performed in Excel and included mean, median, percentages and standard deviation (SD).

RESULTS

We identified 12 (11.8%) cases of discontinuation of dupilumab, either permanently or temporarily, predominantly due to insurance difficulties (58.3%), adverse effects (8.3%), deteriorating disease (8.3%), pregnancy (8.3%), no need for dupilumab (8.3%) and access problems during the COVID-19 pandemic (8.3%).

The mean age was 26.6 years and the median duration of the disease was 20.5 years (SD 5). Most patients had a history of childhood AD (75%). Atopic comorbidities were present in 50% of the patients **(Table 1)**.

Median Dupilumab treatment duration was 9 months (SD 5.6) before suspension. The median follow-up after dupilumab discontinuation was 8 months (SD 3.6). Disease severity before discontinuation was mild (EASI: 2.9). Only 3 (25%) patients who discontinued subsequently reinitiated dupilumab treatment, and 3 (33.3%) patients required immunomodulatory therapy after dupilumab suspension. The mean time without dupilumab before re-initiation was 6.6 months (SD 5.7).

Dupilumab treatment after suspension

Three (33.3%) patients required dupilumab after initial discontinuation. In these patients, the median disease duration was 26.6 years, with a median use of 2 previous immunosuppressants, and all had a history of AD since childhood. The reasons for dupilumab suspension were insurance difficulties (2) and pregnancy (1) **(Table 2)**.

Other systemic treatment after dupilumab suspension

Three (33.3%) patients required immunomodulatory therapy after dupilumab discontinuation without restarting the monoclonal antibody. The median disease duration was 4 years, with a median use of 2 previous immunosuppressants. The reasons for suspension were insurance difficulties (2) and deterioration (1) **(Table 2)**.

No systemic treatment after dupilumab suspension

Six patients, after dupilumab suspension, did not require systemic treatment: 1 required phototherapy and 5 continued only with topical treatment **(Table 3)**. Among these patients, the median disease duration was 23.6 years, with a median use of 1 previous immunosuppressant, and 5 (83.3%) had a history of AD since childhood. The reasons for dupilumab suspension were insurance difficulties (2), adverse effects (1), absence of medical criteria (1) and access problems during the COVID-19 pandemic (2) **(Table 2)**.

DISCUSSION

The current efficacy/safety profile of dupilumab is based on 5-year data, which appears favorable compared to currently used oral immunosuppressive drugs [3, 7].

The reasons for dupilumab suspension in different studies include lack of efficacy, pregnancy, adverse events like AD flares, severe conjunctivitis secondary to dupilumab (frequently between 9 and 20 weeks of treatment), and access difficulties during SARS-COV-2 pandemic. Although there are protocols for maintenance therapy [3, 8-10].

We suggest that some patients who started dupilumab with less difficult-to-treat AD (fewer previous SIMT treatments), fewer atopic comorbidities, and a shorter disease duration may be able to temporarily or permanently discontinue dupilumab, potentially avoiding the need for other systemic therapies. This may result from

	Value Group n= 12
Mean age	26.6 years
Disease duration, median (SD)	20.5 (5)
DA childhood	9 (75%)
Sex	
Male	7 (58.3%)
Female	5 (41.6%)
Atopic comorbidities	6 (50%)
Chronic spontaneous urticaria	0 (0%)
Allergic rhinitis	4 (33.3%)
Asthma	1 (8.3%)
Allergic conjunctivitis	0 (0%)
Food allergy	0 (0%)
Alopecia areata	1 (8.3%)
Other comorbidities	3 (25%)
Systemic (oral or injectable) corticosteroids	7 (58%)
Systemic non-steroidal immunosuppressants or biologic	11 (91.6%)
Cyclosporine	8 (66.6%)
Methotrexate	2 (16.6%)
Azathioprine	6 (50%)
Omalizumab	1 (8.3%)
Phototherapy	6 (50%)
Immunotherapy	1 (8.3%)
Use of immunomodulators	
None	1 (8.3%)
1 immunomodulators	6 (50%)
2 immunomodulators	4 (33.3%)
3 ≥ immunomodulators	1 (8.3%)

Table 1. Demographics characteristics and prior systemic therapy

Variable	Dupilumab restarted (N=3)	No dupilumab restarted (N=9)	
		Systemic treatment after suspension (N=3)	No systemic treatment after suspension (N=6)
Disease duration, mean years	26.6	4	23.6
Time use dupilumab, median	11 months	6 months	11 months
Duration of follow-up, mean, months	2.6 months	7.3 months	8.1 months
Last EASI, median	4	2.8	2.4
Nº of previous Systemic nonsteroidal immunosuppressants, median	2	2	1
Nº of totally of treatment before initiation of dupilumab, median	3.6	3	2
Time between discontinuation and reinitiation, median	6 months	Not apply	Not apply
Childhood AD	1	0.3333	0.8333
Atopic comorbidities	1	0	0.8333

Table 2. Characteristics of post-suspension therapy of dupilumab

Variable	
	Group n = 12
Cause of suspension	
Administrative	7 (58.3%)
Deteriorate	1 (8.3%)
Pregnant	1 (8.3%)
Adverse effects	1 (8.3%)
Medical criteria	1 (8.3%)
Access problems during the COVID-19 pandemic	1 (8.3%)
Post-treatment in no dupilumab restarted	
Other immunomodulatory therapy	3 (25%)
Phototherapy	1 (8.3%)
Topics	5 (41.6%)

Table 3. Variable post-suspension therapy of dupilumab

transcriptional changes in immune and epidermal barrier genes, potentially altering the natural course of the disease [11].

In a real-world, retrospective observational cohort study, high rates of dupilumab persistence were observed (77% at 12 months). Approximately 75% of those who discontinued subsequently reinitiated treatment, on average less than 4 months after discontinuation, with a previous SIMIT use rate of 22.8% in the general cohort [12]. These findings contrast with our results, where only 11.8% discontinued dupilumab, and the mean duration without dupilumab was 6.6 months. Dupilumab re-initiation occurred in only 25% of cases, despite a higher proportion of patients having previously used immunosuppressants (91%), a longer dupilumab treatment duration before discontinuation, and similar rates of atopic comorbidities in our group.

Recent studies suggest extending dupilumab dosing intervals to every 3 to 4 weeks instead of biweekly administration [13-15]. This approach maintains clinical efficacy while reducing treatment costs [13]. However, determining patient suitability and optimal timing for this adjustment remains uncertain. A minimum of 1 year of continuous therapy and excellent clinical response are suggested prerequisites for consideration [13-15].

CONCLUSIONS

We describe a large cohort of patients treated with dupilumab for AD, wherein a smaller subset required re-administration of the monoclonal antibody compared to existing literature.

Controlled clinical trials with a larger number of patients are needed to confirm the likelihood of dupilumab discontinuation due to changes in the natural history of the disease, identifying possible characteristics that may affect the outcome, as described in our cohort: shorter disease duration, fewer atopic comorbidities, and less use of previous systemic immune-modulators.

REFERENCES

1. Awosika O, Kim L, Mazhar M, Rengifo-Pardo M, Ehrlich A. Profile of dupilumab and its potential in the treatment of inadequately controlled moderate-to-severe atopic dermatitis. Clin Cosmet Investig Dermatol. 2018;11:41-9. https://doi.org/10.2147/CCID.S123329

2. Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines. Ann Allergy Asthma Immunol. 2020;124(1):28-35.

3. Beck LA, Thaçi D, Deleuran M, Blauvelt A, Bissonnette R, de Bruin-Weller M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4):567-77.

4. Iuga AO, McGuire MJ. Adherence and health care costs. Risk Manag Healthc Policy. 2014;7:35-44. https://doi.org/10.2147/RMHP.S19801

5. Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med. 2005;353(5):487-97.

6. Damiani G, Calzavara-Pinton P, Stingeni L, Hansel K, Cusano F, "Skin Allergy" Group of SIDeMaST, et al. Italian guidelines for therapy of atopic dermatitis—Adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis). Dermatol Ther. 2019;32(6). https://doi.org/10.1111/dth.13121

7. Beck LA, Deleuran M, Bissonnette R, de Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab Provides Acceptable Safety and Sustained Efficacy for up to 4 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2022;23(3):393-408.

8. Blauvelt A, Bruin-Weller M de, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287-303.

9. Treister AD, Kraff-Cooper C, Lio PA. Risk Factors for Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis. JAMA Dermatol. 2018;154(10):1208-11.

10. Ordóñez-Rubiano MF, Campo I, Casas M. Dupilumab in atopic dermatitis, a protocol for SARS-COV-2-infected patients. Dermatol Ther. 2020;33(6):e14172.

11. Hamilton JD, Suárez-Fariñas M, Dhingra N, Cardinale I, Li X, Kostic A, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014;134(6):1293-300.

12. Silverberg JI, Guttman-Yassky E, Gadkari A, Kuznik A, Mallya UG, Mastey V, et al. Real-world persistence with dupilumab among adults with atopic dermatitis. Ann Allergy Asthma Immunol. 2021;126(1):40-5.

Key points

- Dupilumab cessation was achieved in patients with shorter disease duration, fewer atopic comorbidities, and reduced use of immunosuppressants.
- Despite existing studies on dupilumab dose optimization in atopic dermatitis, little is known about treatment discontinuation and its potential impact on disease modification.

13. Spekhorst LS, Boesjes CM, Loman L, Zuithoff NPA, Bakker DS, Kamphuis E, et al. Successful tapering of dupilumab in patients with atopic dermatitis with low disease activity: a large pragmatic daily practice study from the BioDay registry. Br J Dermatol. 2023;189(3):327-35.

14. Spekhorst LS, Bakker D, Drylewicz J, Rispens T, Loeff F, Boesjes CM, et al. Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis. Allergy. 2022;77(11):3398-407.

15. Patruno C, Potestio L, Fabbrocini G, Napolitano M. Dupilumab dose spacing after initial successful treatment or adverse events in adult patients with atopic dermatitis: A retrospective analysis. Dermatol Ther. 2022;35(12):e15933.