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Dupilumab in HIV-positive patients with atopic dermatitis: a long-term follow-up patient and a literature review

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Abstract

Dupilumab is an IgG4 human monoclonal antibody licensed for the treatment of moderate-to-severe atopic dermatitis. Despite evidence suggesting that T helper type two cytokines can modulate HIV-1 replication and anti-HIV-specific immune responses, impacting on viral reservoirs, HIV-positive patients under immunomodulating therapy have been excluded from clinical trials. We report a 47-year-old HIV-positive man with late-onset severe atopic dermatitis, treated with dupilumab and followed up for 27 months. Improvements in skin lesions and quality of life were observed after four months. Blood tests showed normalization of IgE levels, with the clinical condition remaining stable at a 27- month follow-up. We gathered 16 other cases reported in the literature of HIV-positive patients treated with dupilumab, with no, or few adverse reactions, for which it is unclear if dupilumab should be held accountable. With our case and literature review, we aim to shed light on dupilumab efficacy, safety, and tolerability among HIV-positive patients suffering from atopic dermatitis. In this regard, future research should focus on the effective role, underlying mechanisms, and efficacy of dupilumab in HIV-positive patients and HIV-positivity could be questioned as a valid exclusion criterion for clinical trials.

Keywords: antiretroviral therapy, atopic dermatitis, CD4 count, dupilumab, HIV, viral load

Introduction

Dupilumab, a monoclonal interleukin IL4/IL13 antagonist, is the first biologic drug approved for the treatment of moderate-to-severe atopic dermatitis. Both IL4 and IL13 have proved to possess activity in modulating HIV-1 replication and anti-HIV-specific immune responses, eventually affecting viral reservoirs [1,2]. Nevertheless, in the era of highly active antiretroviral therapy, their effects in HIV-positive patients under immunomodulating therapy are unknown, as this population has been excluded from clinical trials [1]. To date, only a few case reports and case series have been described in the literature, most of which with short duration of follow-up. This review aims to shed light on the efficacy, safety, and tolerability of dupilumab for atopic dermatitis in HIV-positive patients.

Case Synopsis

A 47-year-old man presented for management of late-onset severe atopic dermatitis (**Figure 1A**). The past medical history was positive for HIV infection since 2016, when dolutegravir, abacavir, and lamivudine were started without AIDS-defining conditions. Cycles of topical and systemic corticosteroids were not successful over the years. At physical examination, Eczema Area and Severity Index (EASI) score was 32 and Dermatology Life Quality Index (DLQI) was 22/30. The initial patient-reported Numerical Rating Scale (NRS)-itch was

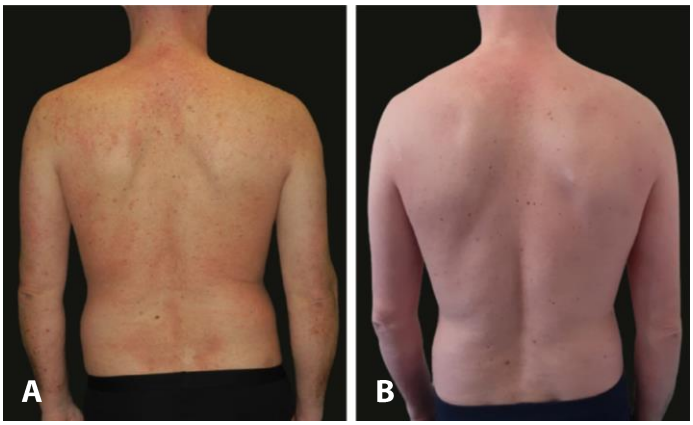

Figure 1. *Generalized erythematous scaly patches with lichenification and excoriations on neck, trunk, and upper limbs **A)** before treatment with dupilumab, and **B)** after 27 months.*

10/10. Baseline blood tests showed a total IgE count of 512 kIU/L. Accordingly, dupilumab therapy was administered with an induction dose of 600mg followed by 300mg every 14 days. The pre-dupilumab viral load was undetectable, the absolute CD4 count was 198 cells/mm^3, and the CD4/CD8 ratio was 0.4.

After four months of therapy, the skin examination showed improvement in lesions (EASI 3.55), in the patient's quality of life (DLQI 6/30, NRS-itch 3/10, NRS-itch 0/10). Blood tests showed a normalization of the IgE count. A reduction in erythema, desquamation, and lichenification on the trunk and limbs were also observed, with persistent lesions only on the face and the neck.

The patient did not develop any side effects and the routine HIV-related parameters remained stable. To date, at the 27-month follow-up, the patient shows a stable clinical condition with EASI 2, DLQI 1 NRS-itch 2/10, NRS-sleep 0 (**Figure 1B**), a persistently undetectable viral load, a CD4 count of 277 cells/mm^3 and a CD4/CD8 ratio 0.7 (**Figure 2**).

Case Discussion

In the last two years, a total of 16 other cases of atopic dermatitis in HIV-positive patients who underwent dupilumab treatment have been published (**Table 1**), [2-10]. The demographic variables can be summarized as follows: 12 patients were males, four were females, all were adults. The general reported dosage of dupilumab was a regimen of 600mg as induction dose followed by 300mg every two weeks, except for the patients of Lor et al. [6] and Nusbaum et al. [10], wherein dupilumab was started with 300mg every other week, without a loading dose. Information on dosage is not available for patients described in three reports [7-9].

The average treatment duration on dupilumab was 10.3 months. The majority of cases (N=15) who underwent biologic treatment for atopic dermatitis had a partial clinical response, whereas in Nusbaum et al. [10] a complete clinical response was observed.

All patients were on antiretroviral therapy and showed increased/stable CD4 count during

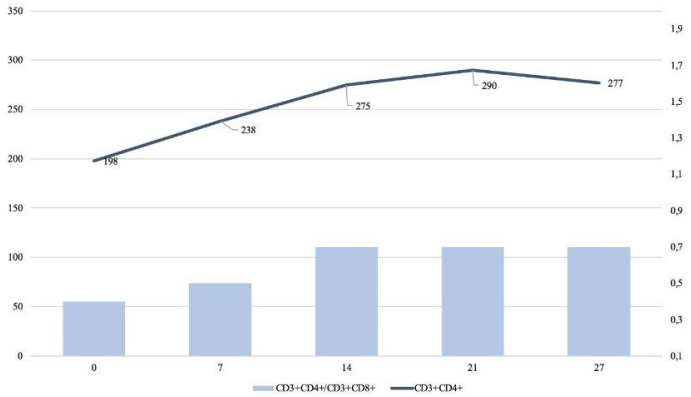

Figure 2. *Immunological markers of our HIV-positive patient treated with dupilumab. Lymphocyte subpopulations were measured by flow cytometry. The X-axis shows the time of the follow-up in months; on the left, the Y-axis displays the absolute value of CD3+ CD4+ T cells, on the right the absolute value of the CD3+CD4/CD3+CD8+ ratio. The line graph illustrates the changes in the absolute value of CD3+CD4+ detected in our patient over a period of 27 months. Overall, CD3+CD4+ increased from month 0 to month 27 throughout the length of the follow-up. Starting at 198 cells/mm^3 at month 0, it steadily grew until 275 cells/mm^3 at month 14 and peaked at 290 cells/mm^3 at month 21. Furthermore, from month 21 to 27 CD3+CD4+ absolute count slightly decreased and stabilized at 277 cells/mm^3. The bar chart shows the CD3+CD4/CD3+CD8+ ratio of our patient during the 27-month follow-up. There was an upward trend in the CD3+CD4/CD3+CD8+ ratio from month 0 to month 14, when it peaked at 0.7. Subsequently, CD3+CD4/CD3+CD8+ ratio remained stable until the end of follow-up. These data are consistent with the absence of infectious side effects in our patient and support the safety profile of dupilumab in HIV-positive patients.*

treatment. Neither viral load changes, nor significant differences in terms of safety and efficacy of dupilumab have been observed according to the different antiretroviral regimens. Also, no drug-drug interactions were reported or expected.

The drug was generally well-tolerated and no serious adverse events have been related to dupilumab administration. One case of mild eye dryness, relieved by lubricating eye drops, has been reported [8]. In Ordònez-Rubiano et al. [9], the patient developed odynophagia and cough owing to a concurrent SARS-CoV-2 infection, which was considered mild and did not require hospitalization. Marks et al. [3] described a painful ulcer on the right perianal skin (herpes simplex virus culture negative) that appeared in a patient with a notable history of anal dysplasia two weeks after the loading dose of dupilumab. A clinical course complicated by parotid gland infection treated with oral cefdinir and an episode of a localized varicella-zoster virus infection on the right abdomen responsive to oral valacyclovir have been described by Lor et al. [6] In the case series of Nusbaum et al. [10], since starting dupilumab, viral warts involving the dorsal hands and the perianal region were detected in two patients. In contrast, another patient reported an upper respiratory tract infection, treated with azithromycin.

To the best of our knowledge, this is the first literature review analyzing all HIV-positive patients affected by atopic dermatitis and treated with dupilumab. Moreover, the 27-month follow-up of our patient is the longest described so far.

Although the number of cases is still limited, we believe that the use of the IL4/IL13 antagonist can be considered a potentially effective choice in HIV-positive patients suffering from moderate/severe atopic dermatitis. Previous evidence has supported a shift from Th1 to Th2 immune response in HIV/AIDS patients. Furthermore, several studies have shown susceptibility to infection and allergic Th2-mediated disorders, with an increased prevalence of both atopic dermatitis and asthma [8]. Accordingly, Patella et al. [11] found that HIV glycoprotein-120 stimulates the release of IL4, which in turn, upregulates the chemokine receptor CXCR4, an important mediator in HIV cellular entry. Thus, these findings suggest that the inhibition of IL4 could play a positive role in the control of HIV.

Conclusion

The results of our analysis are encouraging and not surprising. We recapitulate the efficacy, safety, and tolerability of dupilumab in a cohort of 17 patients, reporting either increased or stable CD4 count. Overall, adverse reactions seem to be mild and it is not clear if dupilumab is actually responsible for them. Although much of our knowledge on dupilumab for atopic dermatitis in HIV-positive patients is based on case reports and case series, our data seem to suggest its potential application in clinical practice, with continuing mandatory monitoring of CD4 count and HIV viral load.

Therefore, HIV positivity as a valid exclusion criterion in the selection of study populations for monoclonal antibody clinical trials might be questioned, given the preliminary evidence shown by this and other monoclonal antibody treatments for several diseases [12]. However, further research and large-scale studies should be carried out to further clarify the effective role, mechanisms, and efficacy of dupilumab in HIV-positive patients.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Cases of atopic dermatitis in HIV-positive patients treated with dupilumab.*

Study	Patients	Treatment duration (months)	CD4 count (cells/mmc)		Viral load (copies/ml)		Chart	Clinical Response	Notes
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment			
Mollanzar et al. [2] (2019	F, 20yrs	4	860	1012	Undetectable	Undetectable	Yes	IGA 4/4 to 1/4 NRSI unreported to 0/10	
	F, 40yrs	4	77	92	276.000	121.000	Yes	IGA 4/4 to 1/4 NRSI 10/10 to 2/10	
Marks et al. [3] (2019)	M, 50yrs	4	665	860	Undetectable	Undetectable	Emtricitabine-tenofovir alafenamide and dolutegravir	IGA 3/4 to 1/4 (after 2 months)	Suspected perianal HSV
Romagnuolo et al. [4] (2020)	F, 52yrs	15	688	738	Undetectable	Undetectable	Dolugetavir,abacavir and lamivudine	EASI 24 to 5 DLQI 9/30 to 2/30 NRSi 9/10 TO 4/10 IgE 3736 to 1460 IU/mL	
Brodksa et al. [5] (2020)	M, 40yrs	8	800	840(4 months)	Not reported	Not reported	Emtricitabine, tenofovir alafenamide, and darunavir	EASI 39 to 1.8, BSA 72% to 6%, SCORAD 82.4 to 16.3, DLQI 12 to 4, VAS 10 to 1 IgE19.000 TO 11800 (4 months)	
Lor et al. [6] (2020)	M, 48yrs	23	1026	952 (4 months) 1003 (15 months)	Undetectable	Undetectable (<20 until 15 months, then undetectable)	Not reported	Not reported	Parotid gland infection and varicella zoster virus infection on right abdomen

				905 (23 months)					(resolved with valacyclovir)
Olbricht et al. [7] (2020)	M, 54yrs	6	603	650	<40	< 40	Dolutegravir, emtricitabine and tenofovir	SCORAD 42.2 to 27.2 DLQI 13 to 2	
Alawadhi et al. [8] (2020)	M, 51yrs	6	837	1001 (6 months)	Undetectable	Undetectable	Yes	BSA 95% to 30% IGA 4 to 1--2	
	M, 42yrs	8	245	259 (8 months)	Undetectable	Undetectable	Yes	BSA 50% to 5% * a 6 mesi IGA 3 to 1 *a 6 mesi	Mild dryness of 1 eye relieved with lubricating eye drops
	M, 59yrs	3	425	594 (3 months)	38	23	Yes	BSA 90% to 40% IGA 4 to 1	
	M, 54yrs	7	701	606 (7 months)	Undetectable	Undetectable		IGA0	
Ordònez-Rubiano et al. [9] (2021)	M, 27yrs	17	600	Stable	Undetectable	Not reported	Yes	SCORAD: 8, EASI: 1, DLQI: 4, POEM: 4 (12 months)	COVID-19 (odynophagia and cough)
Nusbaum et al. [10] (2021)	56yrs	20	684	530 (12 months)	414 (12 months)	40 (12 months)	Bictegravir, emtricitabine and tenofovir	Partial response	Since starting dupilumab, viral warts of dorsal hands were detected
	35yrs	14	136	183 (12 months)	<40	<40 (12 months)	Abacavir, dolutegravir and lamivudine	Partial response	Pre-existing and recurrent perianal viral warts
	68yrs	13	430	482 (12 months)	<40	<40 (12 months)	Efavirenz, emtricitabine and tenofovir	Complete response	
	37yrs	13	735	700 (12 months)	<40	<40 (12 months)	Efavirenz, emtricitabine and tenofovir	Partial response	Since starting dupilumab, upper respiratory infection, treated with azithromycin

Our patient (2021)	M, 47yrs	27	198	277 (27 months)	Undetectable	Undetectable	Dolutegravir, abacavir and lamivudine	EASI 32 to 2 DLQI 22 to 3 NRSi 10 to 2 (after 27 months)	