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Use of dupilumab in patients who are HIV-positive: report of four cases

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DEAR EDITOR, Atopic dermatitis (AD) and prurigo nodularis (PN) are defined by the drive to itch. Indeed, AD is so intensely pruritic, it is described as the itch that rashes. Incidences of AD and PN are higher in patients with HIV, with a prevalence of 30–50% in patients who are HIV-positive, in contrast to a prevalence of 2–5% in seronegative adults.¹ Additionally, approximately 39% of patients with HIV have PN, supporting PN as the most frequent skin disorder in patients who are HIV-positive.¹

Dupilumab, a novel monoclonal interleukin (IL)-4/IL-13 antagonist, is the first biologic approved for the treatment of moderate-to-severe AD. Recent reports have described that dupilumab provides improvement in patients with PN.² Unfortunately, the effects of dupilumab in patients who are HIV-positive are unknown, as these patients were excluded from clinical trials. Herein, we describe four patients with HIV, two with concomitant AD and two with concomitant

PN, that were treated safely and successfully with dupilumab. All patients reported an improvement in the severity of itch as measured by the numerical rating scale for itch intensity (NRSi). Clinical improvement was noted for all patients as measured by the Investigator's Global Assessment (IGA). NRSi, IGA and HIV laboratory values are summarized in Table 1.

Superpotent topical steroids and topical calcineurin inhibitors failed to provide benefit in all patients. Narrowband ultraviolet B failed in patients with schedules that allowed for regular phototherapy sessions. Treatment with dupilumab was initiated using standard dosing regimen of a 600-mg induction dose followed by 300 mg every 2 weeks. No adverse events were reported.

Patient 1 was a man in his 60s with severe PN. The pre-dupilumab viral load was 168 copies mL⁻¹, the absolute CD4 count was 229 cells µL⁻¹ and the CD4/CD8 ratio was 0.16. An initial NRSi of 7/10 was reported by the patient. After 2 weeks of dupilumab, NRSi improved to 4/10. At 1-, 4-, 6- and 9-month follow-ups the patient reported an NRSi of 0/10. Stepwise clinical improvement was noted with dupilumab.

Patient 2 was a man in his 60s with severe PN. The pre-dupilumab viral load was undetectable, the absolute CD4 count was 1058 cells µL⁻¹ and the CD4/CD8 ratio was 0.77. With an initial patient reported NRSi of 10/10, this patient desired more aggressive treatment but also wanted to avoid all frankly immunosuppressive medications, such as prednisone, despite well-controlled HIV. At 1-month follow-up, the patient-reported NRSi improved to 5/10. At 2-, 3- and 6-month follow-ups the NRSi was 0/10.

Patient 3 was a woman in her 20s with severe AD. Pre-dupilumab, the viral load was undetectable, the absolute CD4 count was 860 cells µL⁻¹ and the CD4/CD8 ratio was 2.1. At 2- and 4-month follow-ups, the patient reported an NRSi of 0/10.

Patient 4 was a woman in her 40s with severe AD. As a result of poorly controlled HIV disease, topicals and narrow-band ultraviolet B were attempted for an extended period. After failure to improve and the patient's desire for aggressive

Table 1 HIV disease activity during treatment with dupilumab

Indication	Patient 1 Prurigo nodularis	Patient 2 Prurigo nodularis	Patient 3 Atopic dermatitis	Patient 4 Atopic dermatitis
Pre-dupilumab				
Viral load, copies mL ⁻¹	168	Undetectable	Undetectable	276 000
Absolute CD4 count, cells µL ⁻¹	229	1058	860	77
CD4/CD8 ratio	0.16	0.77	2.1	0.06
IGA	4/4	4/4	4/4	4/4
NRSi	7/10	10/10	Unreported	10/10
Post-dupilumab				
Length of follow-up, months	9	6	4	4
Viral load, copies mL ⁻¹	Undetectable	Undetectable	Undetectable	121 000
Absolute CD4 count, cells µL ⁻¹	188	1206	1012	92
CD4/CD8 ratio	0.22	0.74	2.3	0.07
IGA	1/4	1/4	1/4	1/4
Final NRSi	0/10	0/10	0/10	2/10

IGA, Investigator's Global Assessment; NRSi, numerical rating scale for itch intensity.

therapy, dupilumab was initiated. The pre-dupilumab viral load was 276 k, the absolute CD4 count was 77 cells μL^{-1} and the CD4/CD8 ratio was 0.06. The initial patient-reported NRSi was 10/10. At the 2-week follow-up, AD disease was still severe, but the patient reported an improved NRSi of 7/10. At the 6-week and 4-month follow-ups, the patient reported an NRSi of 2/10.

Our patients experienced rapid and substantial improvements in itch severity while HIV laboratory values remained stable, despite great variance in the degree of HIV disease control. However, laboratory values must be interpreted carefully in the context of accurately reflecting the presence of clinically significant improvements in HIV disease, as count fluctuations in both healthy individuals and those who are HIV-positive are normal.³ Despite interpersonal variations, a change of at least 30% between two absolute CD4 count-test results for a patient on antiretroviral therapy is considered to be significant,⁴ which we did not see. Given the number of patients and the relatively brief follow-up time, we would like to emphasize that the laboratory values do not provide quantitative evidence on the safety of dupilumab in patients who are HIV-positive.

That dupilumab did not patently exacerbate our patients' underlying immunodeficiency is not surprising. A T helper (Th)1/Th2 imbalance is also seen in most patients with HIV, with evidence for increased Th2 responses.⁵ Additionally, HIV-1-glycoprotein-120 is a potent stimulator of IL-4, and indirectly increases virulence.⁶ In both Europe and Nairobi, human resistance to HIV infection has been noted in cohorts with IL-4 genetic variations resulting in a net decrease of IL-4 activity.^{7,8} All suggest that inhibition of IL-4 may be beneficial in the setting of HIV infection.

The marked NRSi and IGA improvements in our patients are promising. Firstly, we recapitulate that dupilumab provides rapid and substantial improvement in both AD and PN. Secondly, the cases of these patients provide preliminary evidence that dupilumab is safe in patients who are HIV-positive and does not instigate disease progression. Our findings point to the necessity for further studies to address this unmet need.

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Mast cell activation in Dowling–Degos disease

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DEAR EDITOR, Dowling–Degos disease (DDD, OMIM 179850) is a rare autosomal-dominant genodermatosis in the spectrum of reticulate pigmented anomalies that usually presents after puberty. It is characterized by reticulate hyperpigmentation and small brownish papules, located in various regions depending on the mutation. Loss-of-function mutations in the genes *KRT5*, *POGLUT1*, *POFUT1* and *PSENEN* have been identified in DDD. Patients with *KRT5* mutations usually develop their lesions in intertriginous areas, whereas patients with *POGLUT1* often show affected extremities. Histology reveals downward elongations of rete ridges with a reticulated or fenestrated pattern, occasional horn cysts and basal hyperpigmentation.¹ The phenotype depends on the affected gene.^{2–6}

Hereby, we report on four female patients with DDD with a negative family history. All of them were referred to our outpatient clinic with itchy brownish papules that started developing after puberty. Itch worsened upon heat in one of the patients, Darier sign and serum tryptase levels were negative in all four patients. In patient A, mutational analysis revealed a *KRT5* mutation [c.418dupA (p.Ile140AsnfsX39)]. The patient showed disseminated small red-brownish papules all over the body with predilection of the submammary and axillary folds.

In the other three patients, mutations in *POGLUT1* were identified. The heterozygous mutation c.1051C>T