Title: A case of hidradenitis suppurativa successfully treated with apremilast in a patient with psoriasis and SAMPUS.

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A case of hidradenitis suppurativa successfully treated with apremilast in a patient with psoriasis and SAMPUS.

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory skin disease mainly affecting sites rich in apocrine glands, such as the axillary, inguinal and anogenital regions.[1] Psoriasis is a chronic inflammatory immune-mediated skin disease, affecting about 2–3% of the Caucasian population, characterized by erythematous scaly plaques and can be associated to severe comorbidities.[2] Apremilast is an oral phosphodiesterase-4 (PDE-4) inhibitor which modulates the expression of several inflammatory cytokines. It is approved for moderate to severe plaque psoriasis and psoriatic arthritis, although recent studies have suggested other potential uses for it in chronic inflammatory skin diseases like HS.[3] The association between HS and psoriasis is not so rare and probably underestimated. Both diseases present an impairment of interleukin (IL)-23/T helper-17 pathway, an IL-12, -23 and TNF-α overexpression and similar comorbidities. The partially shared immunological pathway may explain the good response for cytokines inhibitors in both conditions.[4] Furthermore, apremilast may be safely used in patients with personal history of malignancy, while biologics are not recommended.[5]

We report a case of HS associated to psoriasis, successfully treated with the "off label" use of apremilast in a patient with a history of superficial atypical melanocytic proliferation of uncertain significance (SAMPUS).[6]

A 35-year-old Caucasian man presented to our outpatient clinic with a 4-year history of HS resistant to multiple systemic therapies, based on antibiotics and retinoids, which had been administered for the previous 6 months. Clinical examination revealed inflammatory nodules (>5) and abscesses on the buttocks (Fig. 1A). Clinical and ultrasound severity stages were respectively Hurley Stage IIIand UltraSound HS - Physician Global Assessment (US HS-PGA) 3. To better estimate the baseline grade of inflammation, we also performed a skin biopsy (Figg. 1B, 1C). In addition, the patient was affected by moderate plaque psoriasis (Psoriasis Area Severity Index - PASI 10,2) and, one year before, he had a pigmented lesion excised that was diagnosed as a SAMPUS. Given the clinical history, the patient was administered a dose of 30 mg apremilast twice daily. After 12 weeks of treatment, the patient showed a reduction of both PASI (75% decrease) and US HS-PGA (from 3 to 2) (Fig. 1D). Clinical improvement was also confirmed by a second skin biopsy (Fig. 1E). At the current time, after almost two years, the patient is still successfully under treatment. He has been followed-up every three months, showing no sign of disease worsening (stable PASI and US HS-PGA scores).

The exact mechanism by which apremilast may work in HS is still unknown. In vitro PDE-4 blockade inhibits neutrophil chemotaxis through decreased production of leukotriene B4 and IL-8, lowering the production of multiple pro-inflammatory cytokines including tumor necrosis factor alpha, IL-12, -23, -2, while upregulating the anti-inflammatory cytokine IL-10. This profile is theoretically in excellent accordance with the current understanding of HS pathogenesis.[1] In support

of this, literature reports multiple studies about the use of apremilast for HS treatment.[3] Patient's history of SAMPUS excision did not allow the use of a biological treatment like adalimumab, which is nowadays the only FDA-approved treatment for severe HS and which is also a consolidated agent in the treatment of psoriasis.[5] Our case is remarkable because it highlights the opportunity to use apremilast, and not biologics, in patients with a history of low grade malignancy and concurrent HS and psoriasis. On the other hand, drugs influencing the immune system might have deleterious effects on cancer immunosurveillance, as reported in a case of melanoma relapsed during apremilast therapy.[7] Interestingly, HS signs and symptoms improved faster than psoriasis' ones, with a clinical improvement of HS inflammatory lesions after 6 weeks of therapy, while PASI 75% was reached only after 12 weeks.

Given this, apremilast may represent a valid option for patients with HS who are not eligible for gold standard treatments.

References

1. Goldburg SR, Strober BE, Payette MJ. Hidradenitis Suppurativa: Epidemiology, clinical presentation, and pathogenesis. Part I. J Am Acad Dermatol. 2019 Oct 8. pii: S0190-9622(19)32827-0.
2. Rodríguez-Zúñiga MJM, García-Perdomo HA. Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome. J Am Acad Dermatol. 2017;77(4):657–666.e8.
3. Vossen ARJV, van Doorn MBA, van der Zee HH, et al. Apremilast for moderate hidradenitis suppurativa: Results of a randomized controlled trial. J Am Acad Dermatol. 2019 Jan;80(1):80-88.
4. Kridin K, Shani M, Schonmann Y, et al. Psoriasis and Hidradenitis Suppurativa: A Large-scale Population-based Study. J Am Acad Dermatol. 2018 Nov 28.
5. Crowley J, Thaçi D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). J Am Acad Dermatol. 2017 Aug;77(2):310-317.
6. Roncati L, Piscioli F, Pusiol T. SAMPUS, MELTUMP and THIMUMP - Diagnostic Categories Characterized by Uncertain Biological Behavior. Klin Onkol. Summer 2017;30(3):221-223.
7. Salopek TG. Recurrence of Melanoma after Starting Apremilast for Psoriasis. Case Rep Dermatol. 2017 Aug 3;9(2):108-111.

Figure legend

Figure 1

(A) Multiple nodules and abscesses on buttocks at baseline (HS-PGA 3); (B) Low-power photomicrograph showing epidermis with ortokeratotic and parakeratotic hyperkeratosis, scales and crusts, acanthosis, neutrophilic granulocytic exocytosis; in the dermis, fibrosis is observable, with intense inflammatory infiltration (magnification 4x); C) High-power photomicrograph showing inflammatory infiltration consisting of neutrophilic and eosinophilic granulocytes, histiocytes and multinucleated giant foreign body cells with destruction of pilo-sebaceous units (magnification 40x); D) Multiple nodules and abscesses on buttocks after 12 weeks of apremilast treatment (HS-PGA 2); E) Low-power photomicrograph showing epidermis with slight ortokeratotic and parakeratotic hyperkeratosis; in the dermis, slight edema is observable, with some small vessels and no inflammatory cells (magnification 4x).