SHORT COMMUNICATION

Combination Therapy with Upadacitinib and Acitretin in Recalcitrant Darier Disease: A Case Report

Man YU[1], Xin PENG[2] and Fanlin MENG[1]*

[1]Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China, and [2]Institute of TCM Clinical-Basis Research, Sichuan Academy of Chinese Medicine Sciences, Chengdu, China. *Email: mengfanlin@cdutcm.edu.cn

Submitted May 5, 2026. Accepted after revision Jul 2, 2026
Published Aug 4, 2026. DOI: 10.2340/actadv.v106.adv-2026-0662 Acta Derm Venereol 2026; 106: adv-2026-0662.

Darier disease (DD), or keratosis follicularis, is an autosomal dominant disorder caused by mutations in the ATP2A2 gene, leading to disrupted epidermal calcium signalling and acantholysis (1). Clinically, it presents with greasy, hyperkeratotic papules in seborrheic areas, often accompanied by severe pruritus and malodor. Management is challenging, with oral retinoids (acitretin, isotretinoin) being the mainstay for moderate-to-severe disease. However, their use is limited by mucocutaneous side-effects, teratogenicity and incomplete efficacy (2, 3). Emerging evidence implicates dysregulated immune signalling, particularly the JAK-STAT pathway, in DD pathogenesis. Elevated cytokines (e.g. IL-6, IL-31) and inflammatory infiltrates suggest a role for targeted immunomodulation (4, 5). While recent case reports have described successful treatment with tofacitinib and baricitinib (6, 7), the use of upadacitinib – a selective JAK1 inhibitor – has not been reported in DD. We present a case of refractory DD achieving rapid and sustained remission with upadacitinib combined with acitretin.

CASE PRESENTATION

A 29-year-old Han Chinese male presented with a 10-year history of progressively worsening DD. Physical examination revealed extensive, confluent, hyperkeratotic and verrucous papules and plaques on the forehead, neck and presternal region (**Fig. 1**A). Nail examination showed longitudinal ridging and V-shaped notching. Histopathology confirmed suprabasal acantholysis, dyskeratotic cells (corps ronds and grains) and follicular involvement (**Fig. 2**A–B). Genetic testing was performed via next-generation sequencing (NGS) of a targeted gene panel covering the entire coding regions and exon–intron boundaries of ATP2A2. This identified a known heterozygous missense mutation, c.2300A>G (p.Asn767Ser), in the patient. The patient reported no family history of DD or other chronic dermatoses, consistent with a de novo occurrence of the ATP2A2 mutation. Prior treatments included high-potency topical corticosteroids, topical retinoids and oral acitretin (30 mg/day for 6 months), which provided partial relief but were limited by xerosis and recurrent flares. At baseline, the patient reported severe pruritus and pain (Visual Analogue Scale [VAS] 8/10), with a modified Darier's Disease Severity Index (mDDI) of 12 and Dermatology Life Quality Index (DLQI) of 18.

Therapeutic intervention and assessment

After obtaining informed consent and institutional approval, the patient was started on upadacitinib 15 mg daily combined with acitretin 20 mg daily. Baseline laboratory tests (CBC, LFTs, lipids) were normal. Month 1: Marked reduction in pruritus (VAS 2/10) and lesion erythema. Plaques began to flatten (Fig. 1B).

Month 3: Near-complete resolution of pruritus and pain (VAS 0/10). mDDI decreased to 3, DLQI to 4.

Hyperkeratosis significantly diminished (Fig. 1C).

Month 6: Acitretin was tapered and discontinued. The patient maintained remission on upadacitinib monotherapy, with only mild textural changes residual (Fig. 1D). No laboratory abnormalities or adverse events (e.g. infection, acne) were observed.

DISCUSSION

This case demonstrates the efficacy of upadacitinib, a selective JAK1 inhibitor, in combination with acitretin for refractory DD. The rapid response (within 1 month) and sustained remission after retinoid withdrawal highlight the potential of JAK inhibition as a steroid-sparing, targeted therapy.

The pathophysiology of DD involves not only calcium dyshomeostasis but also significant inflammatory dysregulation. Studies have shown increased levels of IL-6, IL-23 and IL-31 in DD lesions, all of which signal through JAK-STAT pathways (4, 5). Upadacitinib's selectivity for JAK1 may preferentially block γc-cytokine signalling (e.g. IL-6, IL-31) while minimizing JAK2/JAK3-related side-effects, explaining both the efficacy and favourable tolerability observed (8, 9).

Our findings align with emerging reports of JAK inhibitor efficacy in DD. Behrangi et al. reported successful treatment with tofacitinib (6), while Busto Leis et al. documented baricitinib response (7). However, this is the first report of combination therapy with upadacitinib and acitretin for refractory DD (10), and the first to describe a dual-pathway strategy combining a JAK1 inhibitor with a retinoid.

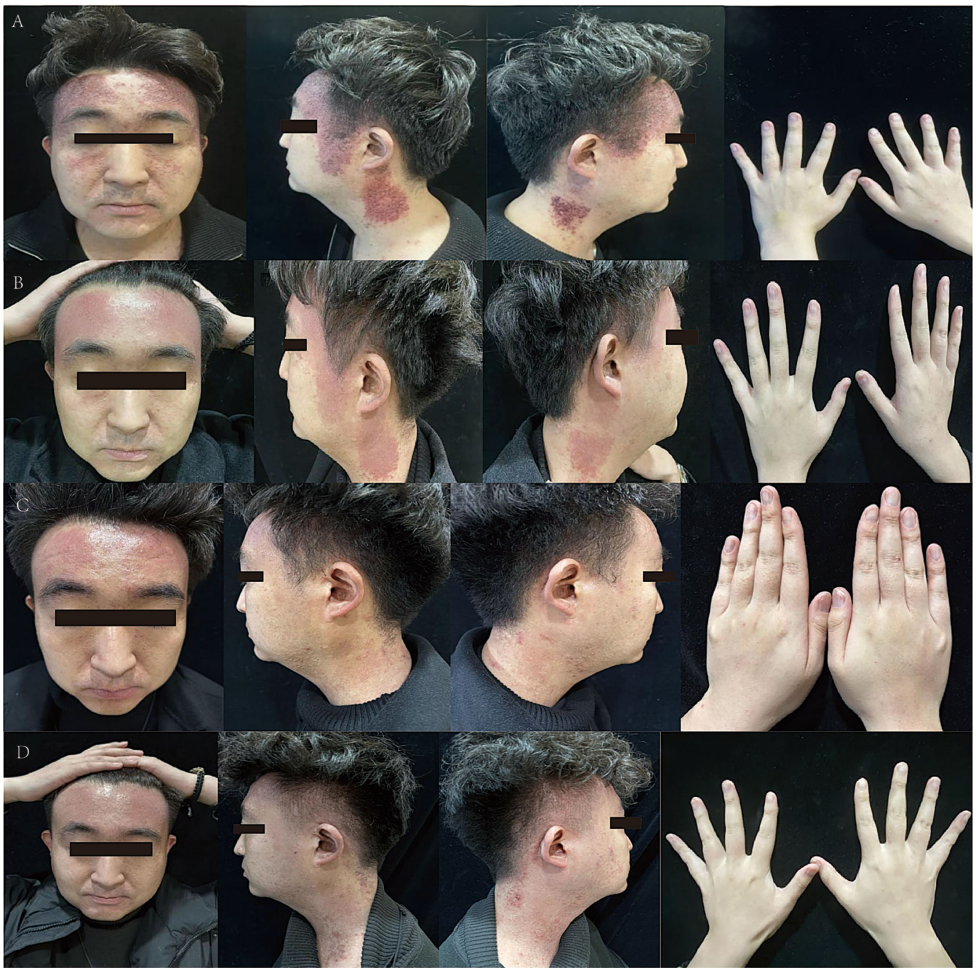

Fig. 1. Clinical course of refractory Darier's disease treated with upadacitinib and acitretin. (A) Baseline: Extensive hyperkeratotic plaques on forehead and neck. (B) Month 1: Reduction in erythema and plaque height. (C) Month 3: Near-complete resolution of hyperkeratosis. (D) Month 6: Sustained remission on upadacitinib monotherapy.

The ATP2A2 mutation identified in our patient (p.Asn767Ser) differs from those previously reported in JAK inhibitor-treated DD cases. For instance, Behrangi et al. did not specify the mutation in their tofacitinib-treated patient (6), while Busto Leis et al. reported a different mutation in their baricitinib-responsive case (7). Our finding adds to the growing evidence that JAK inhibitor efficacy may be independent of the specific ATP2A2 mutation site, suggesting a common downstream anti-inflammatory mechanism. Further studies correlating genotype with therapeutic response are warranted.

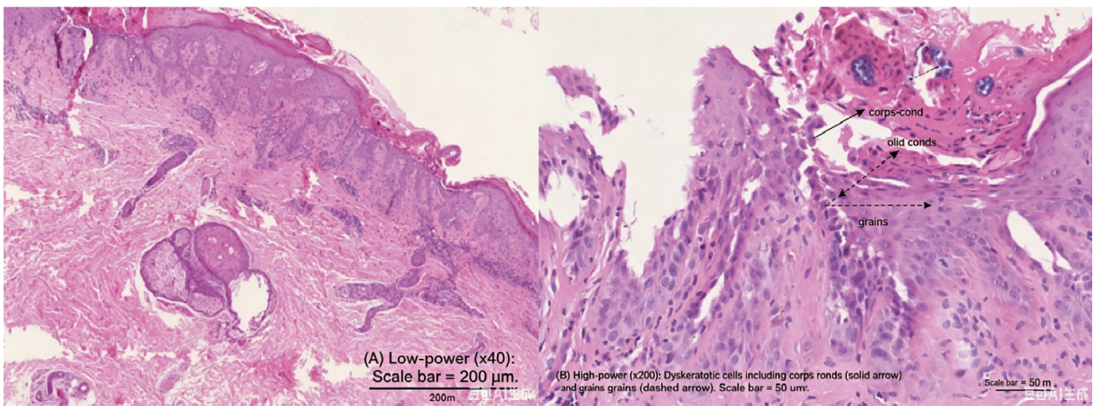

Fig. 2. Histopathological features (H&E). (A) Low-power (X40): Suprabasal acantholysis and cleft formation. Scale bar=200 µm. (B) High-power (x200): Dyskeratotic cells including corps ronds (solid arrow) and grains (dashed arrow). Scale bar=50 µm.

The ability to discontinue acitretin after 6 months suggests that JAK inhibition may effectively maintain remission, reducing long-term retinoid toxicity (3).

Limitations include the single-case design and short follow-up. Larger, controlled studies are needed to confirm efficacy and safety. However, for patients with refractory DD, upadacitinib represents a promising novel option.

Learning points

Novel Mechanism: Upadacitinib, a selective JAK1 inhibitor, can induce rapid and sustained remission in refractory Darier's disease, possibly by targeting IL-6/IL-31-mediated inflammation.

Combination Strategy: Initial combination therapy with low-dose acitretin and upadacitinib may achieve rapid control, allowing for subsequent retinoid tapering and reduction of long-term side-effects.

Retinoid-Sparing: JAK inhibition may serve as a steroid- and retinoid-sparing maintenance therapy for severe DD, particularly in cases resistant to conventional treatments.

ACKNOWLEDGEMENTS

Funding sources: This report was funded by Sichuan Provincial Academy of Traditional Chinese Medicine 2023 Annual Young Talent Two-Year Foundation Building Project, QNCJ-PX-09.

Data availability statement: De-identified data are available from the corresponding author upon reasonable request.

Ethics committee: Written informed consent was obtained from the patient for publication and use of images. The study was approved by the institutional ethics committee.

The authors have no conflicts of interest to declare.

REFERENCES

1. Stefani C, de Gemmis P, Cattelan P, Tibaudo L, Stagni C, De Sensi E, et al. Expanding the spectrum of Darier Disease variants: 13 novel ATP2A2 genetic variations discovered in an Italian retrospective analysis. Gene 2026; 990: 150071. https://doi.org/10.1016/j.gene.2026.150071
2. Zhou MH, Stirrat TP, Edminister JR, Elston DM, Jorizzo J, Motaparthi K, et al. Acantholytic disorders: Update on pathophysiology, diagnosis, and management. J Am Acad Dermatol 2026; 95: 138–147. https://doi.org/10.1016/j.jaad.2026.02.074
3. Dessinioti C, Katsambas A. Vitamins and the skin: Vitamin A and retinoids in dermatology. Clin Dermatol 2026; 44: 212–222. https://doi.org/10.1016/j.clindermatol.2026.02.005
4. Beyens A, Speeckaert R. Transient responses to biologic therapy in Darier disease: consider the role of dysbiosis-driven inflammation. J Eur Acad Dermatol Venereol 2026; 40: 351–352. https://doi.org/10.1111/jdv.70283
5. Wu Z, Lian G, He L, Hu P, Guo Y, Su Z. Targeting JAK-STAT signaling for autoimmune diseases: current understanding, clinical advances, and emerging directions. Immunol Cell Biol 2026; 104: 172–191. https://doi.org/10.1111/imcb.70078
6. Behrangi E, Dehghani A, Zeinali R, Amiri S. Darier's disease successfully treated with tofacitinib: a case report. Case Rep Dermatol 2025; 17: 574–579. https://doi.org/10.1159/000548764
7. Busto Leis JM, Negre GS, Mayor Ibarguren AP, Pinto PH. Response of Darier disease following treatment with baricitinib. JAMA Dermatol 2022; 158: 699–701. https://doi.org/10.1001/jamadermatol.2022.1021
8. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov 2017; 16: 843–862. https://doi.org/10.1038/nrd.2017.201
9. Parmentier JM, Voss J, Graff C, Schwartz A, Argiriadi M, Friedman M, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). BMC Rheumatol 2018; 2: 23. https://doi.org/10.1186/s41927-018-0031-x
10. Sun Z, Bao L. A case of Darier disease with p.N767S mutation in ATP2A2 successfully treated with upadacitinib. Am J Dermatopathol 2026; 48: 410–411. https://doi.org/10.1097/DAD.0000000000003242