OBSERVATION

Low-Concentration Topical Trametinib for Refractory Darier Disease

Darier disease (DD), also known as *ATP2A2*-related syndromic epidermal differentiation disorder, is an inherited acantholytic dermatosis caused by variants in *ATP2A2*, the gene that encodes sarco/endoplasmic reticulum calcium ion (Ca^{2+})-positive-adenosine triphosphatase 2 (SERCA2).[1] Reduced SERCA2 activity leads to impaired endoplasmic reticulum (ER) Ca^{2+} homeostasis, defective keratinocyte adhesion, and relapsing hyperkeratotic eruptions.

Report of a Case | A woman in her 20s presented with persistent, symptomatic truncal DD. Physical examination revealed numerous erythematous-to-brown, keratotic papules, some excoriated and crusted, that were coalescing into plaques on the trunk and cervical region (**Figure 1**, A and B). Histopathology showed suprabasal acantholysis and dyskeratosis (**Figure 2**). Prior therapies included topical keratolytics, corticosteroids, and retinoids, as well as intermittent systemic antibiotics, without sustained disease control.

Given refractory disease, topical trametinib was initiated as monotherapy at 0.02% (5 crushed 2-mg commercial tablets in 50 g of petrolatum), which was applied twice daily to affected areas. Written informed consent was obtained for off-label use. The patient reported symptomatic improvement within days, including complete resolution of pruritus. At 6 weeks, there was marked reduction in erythema, crusting, and hyperkeratosis, with flattening of papules and plaques (Figure 1, C and D), and improvement was maintained at 6 months. No local or systemic adverse effects were observed, and laboratory test results (complete blood cell count, liver enzyme levels, creatine kinase levels, kidney function, and electrolytes) remained within normal limits.

Pathobiologically, SERCA2 loss reduces ER Ca^{2+} stores and disrupts Ca^{2+}-dependent junctional assembly and differentiation programs, weakening epidermal cohesion. In a human organotypic DD model, Zaver et al[2] demonstrated loss and mislocalization of key junctional/desmosomal and cytoskeletal components together with mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway hyperactivation, evidenced by ERK hyperphosphorylation (pERK). Lesional biopsy specimens from patients with DD repeated the same signature, linking the organotypic findings to the disease state in humans.[2] In that system, mitogen-activated protein kinase kinase (MEK) inhibition (including trametinib) reduced pERK and rescued adhesive

Figure 1. Clinical Images of Improvement After Topical Trametinib

Baseline hyperkeratotic papules and plaques on the upper back (A) and anterior chest (B). C and D, Substantial clinical improvement following application of topical trametinib, 0.02%, twice daily for 6 weeks.

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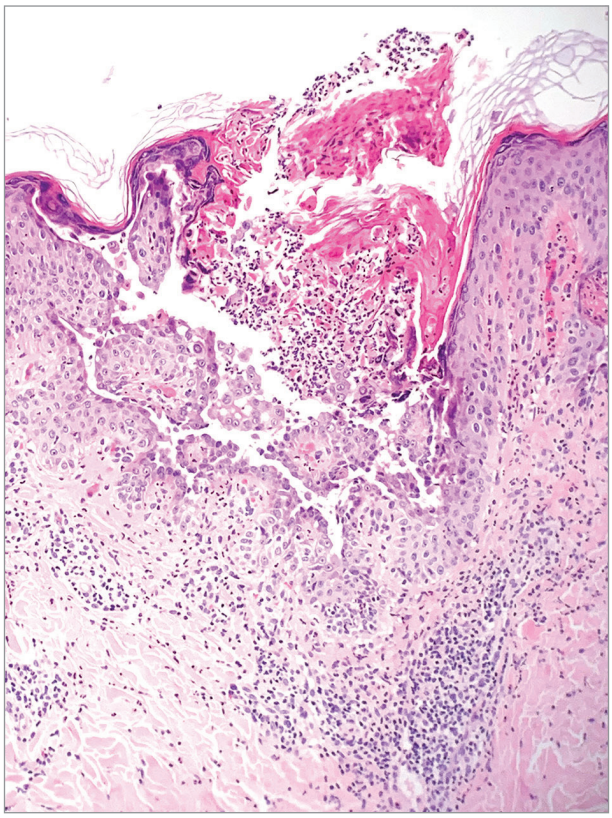
Figure 2. Histopathological Image



Hematoxylin-eosin staining shows suprabasal acantholysis and dyskeratotic keratinocytes (original magnification ×100).

protein expression and keratinocyte integrity despite SERCA2 impairment, providing therapeutic rationale.[2]

Consistent with this rationale, our group recently reported improvement in a patient with severe DD who was treated with oral trametinib, giving support to ERK-pathway modulation translating into clinically relevant disease control.[3] Together, patient-tissue biology, organotypic rescue experiments, and early clinical responsiveness strengthen MEK inhibition as a rational, pathway-directed approach in DD.[2,3]

Topical MEK inhibition may refine this strategy by concentrating pharmacologic activity in the skin while potentially reducing systemic exposure and the monitoring burden associated with oral trametinib, whose labeling highlights clinically important adverse effect risks (including cardiac and ocular events and systemic toxic effects). The optimal concentration and base for topical trametinib are not well known. The concentration used for this patient (0.02%) is 50-fold lower than the 1% preparations reported for dermatologic mosaic rat sarcoma virus/MAPK–driven lesions and other off-label dermatologic uses.[4] Topical trametinib has been compounded as 1% to 2% creams (often with permeation-enhancing components) for epidermal/sebaceous nevi and as a 1% cream for agminated Spitz nevi. Regarding safety, in a phase 1 rosacea study, a tablet-derived trametinib, 0.01%, cream (0.1 mg/g; 0.05 mg in 0.5 mL applied daily) demonstrated no detectable systemic absorption over 21 days.[5] In our setting, the absence of compounding-grade trametinib powder required tablet-based compounding, and feasibility led us to a low-strength formulation (0.02%). For the extent of involvement in this patient, twice-daily application required approximately 150 g of compounded cream per month, prepared from 15 two-mg trametinib tablets (30 mg total). Although this represents half the cumulative oral amount over a comparable period, systemic exposure is expected to be minimal.

This case provides preliminary evidence that low-concentration topical trametinib may be a biologically plausible option for selected patients with refractory DD. However, larger case series and controlled studies are needed to further evaluate the safety, reproducibility, and therapeutic efficacy of this treatment.

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1. Dodiuk-Gad RP. Darier disease is a syndromic epidermal differentiation disorder. *Br J Dermatol*. 2026;194(3):600-601. doi:10.1093/bjd/ljaf468

2. Zaver SA, Sarkar MK, Egolf S, et al. Targeting *SERCA2* in organotypic epidermis reveals MEK inhibition as a therapeutic strategy for Darier disease. *JCI Insight*. 2023;8(18):e170739. doi:10.1172/jci.insight.170739

3. Soto-García D, Dávila-Seijo P, González-Moure C, et al. Trametinib as a promising therapy for Darier disease: case report. *Br J Dermatol*. 2025;193(2):339-341. doi:10.1093/bjd/ljaf160

4. Parsons L, Chen A, Bertus B, et al. Topical trametinib for agminated Spitz nevi harboring *HRAS* mutation. *Pediatr Dermatol*. 2025;42(4):841-843. doi:10.1111/pde.15903

5. Wladis EJ, Busingye J, Saavedra LK, Murdico A, Adam AP. Safety and tolerability of topical trametinib in rosacea: results from a phase I clinical trial. *Skin Health Dis*. 2024;4(2):e346. doi:10.1002/ski2.346

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