Two percentLovastatin ointment as a pathogenesis-directed monotherapy for porokeratosis

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INTRODUCTION
Porokeratosis is a clonal disorder of keratinization associated with heterozygous mevalonate pathway gene mutations. Many clinical variants have been described, with disseminated superficial actinic porokeratosis being the most common one. Skin lesions result from somatic second-hit mutations in MVK, MVD, or PMVK, resulting in decreased expression of the respective enzymes.1–3 Enzyme deficiency is thought to lead to an insufficiency of the end product of the pathway, cholesterol, and the accumulation of upstream metabolites. Recent evidence has demonstrated the efficacy of a pathogenesis-based topical therapy with combined lovastatin/cholesterol therapy in patients with disseminated superficial actinic porokeratosis, linear porokeratosis, and porokeratosis plantaris, palmaris, et disseminata.3 Here, we describe a patient with familial porokeratosis of the disseminated superficial actinic porokeratosis variant who was successfully treated with lovastatin monotherapy.

CASE REPORT
A 36-year-old man presented with small, thin, erythematous plaques surrounded by vague keratotic edges distributed over his upper and lower extremities. The lesions first appeared 18 years before. His family history was significant for disseminated superficial actinic porokeratosis in his father; porokeratosis plantaris, palmaris, et disseminata in his sister and cousin; and squamous cell carcinoma in the latter. The patient received a diagnosis of disseminated superficial actinic porokeratosis, and whole-exome sequencing revealed a heterozygous c.70+5G>A mutation in the MVD gene.

He began receiving 2% cholesterol/2% lovastatin ointment applied twice daily to the upper aspect of his left limb. The patient experienced significant improvement in erythema and scaling of lesions after 4 weeks of therapy. He also began receiving 2% cholesterol ointment applied twice daily to previously untreated areas. However, no clinical improvement was noted in areas exposed to cholesterol monotherapy after 4 weeks.

The patient had untreated lesions in his lower extremity and we wondered whether lovastatin monotherapy would be efficacious. We hypothesized that blocking the mevalonate synthesis pathway upstream of the MVD enzyme would be sufficient to alleviate his symptoms by preventing the accumulation of mevalonate pathway metabolites. The patient was informed of possible adverse effects of the treatment and his verbal informed consent was obtained. He began receiving lovastatin 2% ointment applied twice daily. A remarkable decrease in scaling was noted after 4 weeks of therapy. After 6 weeks of therapy, he achieved complete response (Fig 1). The treatment was well tolerated, with no erythema or pruritus reported.

DISCUSSION
Lesions of porokeratosis have been associated with the development of squamous and basal cell carcinomas.4 Porokeratosis treatment had proven challenging, with various topical and systemic treatments used with limited success until recently.5 Mutations in mevalonate synthesis pathway genes...
have been known to cause porokeratosis, and our group recently demonstrated that combined lovastatin/cholesterol therapy can successfully treat disseminated superficial actinic porokeratosis; porokeratosis plantaris, palmaris, et disseminata; and linear porokeratosis.3 It is theorized that a disruption of the mevalonate pathway functionally leads to a deficiency in cholesterol production, with accumulation of toxic upstream metabolites. The reasoning underlying the combined therapy is to inhibit synthesis and accumulation of upstream metabolites by using a statin while replenishing cholesterol. Prompted by our previous results, we hypothesized that blocking the accumulation of mevalonate pathway metabolites without replenishing the end product of the pathway would result in clinical improvement. Here, we showed that lovastatin monotherapy can successfully treat disseminated superficial actinic porokeratosis, whereas topical cholesterol monotherapy does not.3

Lesions in our patient completely resolved within a timeframe similar to that with lovastatin/cholesterol combination therapy, and no adverse effects were noted. Given that lovastatin/cholesterol led to lesion improvement in patients with porokeratosis plantaris, palmaris, et disseminata and linear porokeratosis, these variants may also be amenable to lovastatin monotherapy.3 Topical statin monotherapy has also been shown to be effective in treating cutaneous manifestations of congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, an X-linked dominant disorder of distal cholesterol metabolism.9 As observed in our patient, cholesterol monotherapy does not lead to symptom improvement in patients with congenital hemidysplasia with ichthyosiform erythroderma and limb defects syndrome.7

3-hydroxy-3-methyl-glutaryl-CoA reductase is responsible for the synthesis of mevalonate. Statins inhibit the activity of this enzyme, thereby leading to a decrease in mevalonate levels. Statins have been shown to possess anti-inflammatory properties even with topical application.8 The mechanisms underlying these properties have begun to be identified. Evidence has demonstrated that mevalonate accumulation can result in the activation of the innate immune response and increased cytokine production.9 These proinflammatory effects were mitigated by statins. These results suggest that the activation of the immune response by mevalonate pathway metabolites may contribute to the development of porokeratosis. Hence, topical statin therapy in disseminated superficial actinic porokeratosis likely acts as a local innate immunity overactivation inhibitor by preventing mevalonate accumulation.

Taken together, the results in our patient suggest that the accumulation of intermediates in the mevalonate synthesis pathway, not cholesterol deficiency, is the primary mechanism driving disseminated superficial actinic porokeratosis lesions. Hence, future studies aimed at further delineating the effect of mevalonate pathway mutations in porokeratosis should focus on the accumulation of upstream intermediates such as mevalonate.

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Fig 1. Clinical manifestation before and after topical lovastatin ointment treatment. Before treatment, there were circular, well-circumscribed papules with a hyperkeratotic rim on the right lower extremity. The lesions resolved completely after 6 weeks of 2% lovastatin ointment monotherapy. The patient shaved his shin before treatment initiation.
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