Topical cholesterol/lovastatin for the treatment of porokeratosis: A pathogenesis-directed therapy

Lihi Atzmony, MD,a,b,c Young H. Lim, BS,a,b,d Claire Hamilton, MD, PhD,a Jonathan S. Leventhal, MD,a Annette Wagner, MD,e,f Amy S. Paller, MD,e,f and Keith A. Choate, MD, PhD,a,b,d
New Haven, Connecticut; Tel Aviv, Israel; and Chicago, Illinois

Background: Porokeratosis is associated with mevalonate pathway gene mutations. Therapeutic options are few and often limited in efficacy. We hypothesized that topical therapy that aims to replenish cholesterol, an essential mevalonate pathway end-product, and block the accumulation of mevalonate pathway toxic metabolites could alleviate porokeratosis.

Objective: To study the efficacy of topical cholesterol/lovastatin in different variants of porokeratosis.

Methods: We enrolled a series of 5 porokeratosis patients,1 with disseminated superficial actinic porokeratosis, 2 with porokeratosis palmaris et plantaris disseminata, and 2 with linear porokeratosis. Patients were genotyped before initiation of therapy. Patients then applied topical cholesterol/lovastatin twice daily to a unilaterally defined treatment area for up to 3 months. The response was evaluated and patients photographed at every visit.

Results: Three patients had MVD mutations, and 2 patients had PMVK mutations. Treatment with topical cholesterol/lovastatin (but not cholesterol alone) resulted in near complete clearance of disseminated superficial actinic porokeratosis lesions after 4 weeks of therapy and moderate improvement of porokeratosis palmaris et plantaris disseminata lesions and linear porokeratosis lesions. There were no adverse events.

Limitations: Case series design with a small number of patients.

Conclusion: Topical cholesterol/lovastatin is an effective and well-tolerated therapy for porokeratosis that underscores the utility of a pathogenesis-based therapy that replaces deficient end products and prevents accumulation of potentially toxic precursors. (J Am Acad Dermatol 2020;82:123-31.)

Key words: cholesterol; disseminated superficial actinic porokeratosis; genetics; genetic skin diseases; linear porokeratosis; medical dermatology; mevalonate pathway; pediatric dermatology; porokeratosis; statins; therapy; topical therapy.

Porokeratosis is a heterogeneous group of keratinization disorders subclassified on the basis of clinical appearance. Variants include disseminated superficial actinic porokeratosis (DSAP), disseminated superficial porokeratosis, porokeratosis of Mibelli, porokeratosis palmaris et plantaris disseminata (PPPD), and linear porokeratosis (LP). All variants share the histopathologic

From the Department of Dermatologya and Department of Genetics,b Yale University School of Medicine, New Haven; Sackler Faculty of Medicine, Tel Aviv Universityc; Department of Pathology, Yale University School of Medicine, New Havend; and Department of Dermatologyb and Department of Pediatics,b Northwestern University Feinberg School of Medicine, Chicago.

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Reprint requests: Keith A. Choate, MD, PhD, Departments of Dermatology, Genetics, and Pathology, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520. E-mail: keith.choate@yale.edu.
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feature of a cornoid lamella, a vertical column of parakeratosis situated above dyskeratotic cells within the granular layer.13 Familial cases, with an autosomal dominant mode of inheritance, and sporadic cases have been described.2-4 DSAP is the most common subtype of porokeratosis, although its exact prevalence is unknown. This type usually affects individuals in their 30s and 40s and has a slight female predominance. Lesions appear on sun-exposed areas as asymptomatic or pruritic pink-to-brown papules or plaques with a raised railroad track border and an atrophic, sometimes hypopigmented center.

Porokeratosis is considered a premalignant condition with a malignant transformation rate of 7.5%.5 The most common reported malignancy is squamous cell carcinoma, but basal cell carcinomas and melanomas have also been reported.6,7 Although all subtypes of porokeratosis have an increased risk of skin cancer, linear, large, and long-standing lesions are reported to have higher risk.5

As in other clonal keratinocyte disorders, treatment for porokeratosis is primarily focused on lesion destruction by using cryotherapy, photodynamic therapy, carbon dioxide lasers, 5-fluorouracil, or a combination of these therapies.8 Other strategies to reduce scale and inflammation associated with these lesions include acitretin, topical corticosteroids, and vitamin D analogs.8 These approaches are often ineffective and costly.

Recently, heterozygous germline mutations in the mevalonate pathway genes MVK, PMVK, MVD, and FDP5 have been identified in familial and sporadic porokeratosis,2,3,9 and second-hit somatic mutations were identified in DSAP and linear porokeratosis.10,11 Together, these findings suggest that individual lesions in various porokeratosis variants arise in regions affected by second-hit mutations in the genes encoding key components of the mevalonate pathway.

The mevalonate pathway is essential for cell growth and differentiation, gene expression, cytoskeleton assembly, and posttranslational modification of proteins involved in intracellular signaling (Fig 1).12,13 Cholesterol, an end product of the mevalonate pathway, is a key component of the extracellular lipid matrix in the stratum corneum, playing an essential role in providing and maintaining skin barrier function. Depletion of cholesterol has been reported to result in increased sensitivity of keratinocytes to stimuli driving apoptosis.14 Premature apoptosis and dysregulated keratinocyte differentiation have been identified in several types of porokeratosis,6,15 supporting a simple pathogenesis model in which loss-of-function mutations in MVK, PMVK, MVD, and FDP5 result in cholesterol deficiency in porokeratosis-affected skin, directly leading to the disease phenotype. However, as has been demonstrated in other inherited metabolic disorders,16-18 the porokeratosis phenotype might reflect both deficiency in the metabolic pathway end products and the accumulation of toxic metabolites synthesized proximally in the pathway.

Genetic insights into the pathogenesis of porokeratosis provide guidance for pathogenesis- or mechanism-directed therapies that can aim to correct the metabolic anomalies resulting from diminished mevalonate pathway enzyme activity. A therapeutic approach preventing the accumulation of toxic metabolites while replenishing essential end products has been utilized in congenital hemidystasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, an X-linked dominant disorder of distal cholesterol metabolism. Topical application of lovastatin, a hydroxymethylglutaryl coenzyme A inhibitor, and cholesterol led to significant improvement of skin lesions, while application of cholesterol alone (ie, solely product replenishment) did not correct the phenotype.16 The topical application of the dual regimen enabled lovastatin to bypass the first-pass effect of statin metabolism in the liver (which happens with systemic administration) and provided direct access of keratinocytes to cholesterol for efficient transepidermal incorporation.19,20

Given our knowledge of the contribution of mevalonate pathway dysfunction in the development of porokeratosis, we hypothesized that applying topical cholesterol/lovastatin could alleviate porokeratosis by both replenishing cholesterol and blocking the accumulation of mevalonate pathway toxic metabolites. We tested the application of topical cholesterol/lovastatin on patients with PPPD, DSAP, and LP.

**CAPSULE SUMMARY**

- Porokeratosis is primarily associated with mevalonate pathway gene mutations.
- We tailored and tested a pathogenesis-directed therapy for porokeratosis that was based on the putative roles of pathway end-product (cholesterol) deficiency and toxic metabolite accumulation on affected skin. This therapy, topical cholesterol/lovastatin, was found to be effective for different variants of porokeratosis.
MATERIAL AND METHODS

Participants and genetic analysis

The genetic investigation was approved by the Yale Human Investigation Committee and complies with the declaration of Helsinki principles. Individual consent was obtained in writing from all participants. Genomic DNA was isolated via standard phenol-chloroform extraction from peripheral blood or saliva. We obtained genomic DNA from fresh, full-thickness skin biopsies; 1-mm affected epidermis cores from formalin-fixed paraffin-embedded specimens; or cultured keratinocytes from affected skin using the DNeasy Micro Kit (QIAGEN, Hilden, Germany), with deparaffinization performed in addition for the formalin-fixed paraffin-embedded specimens. Paired analysis of whole-exome sequencing of affected skin with blood or saliva were performed as previously described. Mutations were confirmed with Sanger sequencing. Patients were offered treatment with topical cholesterol/lovastatin after discussion of potential adverse events and provided verbal informed consent to therapy.

Treatment

A 2% cholesterol/2% lovastatin ointment (n = 4) or lotion (n = 1) was applied twice a day on lesional skin with occlusion for the first 1-2 weeks depending on skin lesion thickness. Therapy continued for 6 weeks-3 months. All patients were allowed to use emollients on untreated skin. One patient (identification no. FP100-1) applied 2% cholesterol ointment twice a day for 4 weeks on lesional skin that was not treated with 2% cholesterol/2% lovastatin. Patients were examined at 3-4-week intervals and up to 5 weeks-3 months for clinical response.

Assessment of clinical response

Clinical photography was performed and a biopsy of affected skin was obtained at baseline. Erythema, scaling, thickness, size, and number of lesions were evaluated at every visit. Photography was performed at each visit to document clinical response.

RESULTS

Clinical and histologic description of cases

Three patients with familial porokeratosis and 2 patients with LP were included in our cohort. Patients with familial porokeratosis belonged to the same family but varied in their clinical presentation. Patient characteristics are detailed in Table I. Patient FP100-1 had DSAP with small, thin erythematous plaques surrounded by vague keratotic edges distributed over sun-exposed aspects of the upper and lower limbs. His sister (FP100-6) and cousin (FP100-9) had a clinical presentation of PPPD, with punctate papules over pressure areas of the soles and larger purple-brown thin plaques with atrophic centers and more-pronounced keratotic borders distributed over the extremities. The medical history of FP100-9 included cutaneous squamous cell carcinoma (Table I).

Patient LP1 was a 5-year-old girl with extensive whorled-linear, scaly, thick pink pruritic plaques over the left side of her body since birth. Patient LP2 was a 20-year-old man with whorls of linear, pink verrucous papules and plaques on his upper extremities and left lower extremity that appeared at birth and became thicker over time. In both, there was no family history of porokeratosis. In all patients, a coronoid lamella was evident upon histopathologic evaluation.

Genetic analysis

Whole-exome sequencing was conducted on affected and unaffected participants of the familial porokeratosis group, which lead to the identification of a heterozygous MVD c.70+5G>A mutation (Table I). The variant cosegregated with disease and was recently found by our group in a patient with LP, where it was shown to affect MVD splicing. Paired analysis of blood and affected keratinocytes did not identify somatic mutations or loss of heterozygosity (Table I). Paired whole-exome sequencing of affected tissue and blood from LP1 and LP2 identified germline and somatic PMVK mutations (Table I).

Response to therapy

FP100-1, FP100-6, FP100-9, and LP2 applied a 2% cholesterol/2% lovastatin ointment twice daily, and LP1 applied a 2% cholesterol/2% lovastatin lotion twice daily. All familial porokeratosis patients applied the ointment on 1 limb (FP100-1 left upper limb, FP100-6 right shin, FP100-9 right thigh). LP1 applied the lotion on the left side of the trunk and LP2 applied the ointment on the left upper limb.
Fig 1. The mevalonate pathway. The mevalonate pathway is an essential metabolic pathway that uses acetyl-CoA to produce sterols and isoprenoid metabolites that are essential for a broad range of metabolic processes. Genes previously found to be involved in porokeratosis are **bolded**. Asterisks mark the genes in which mutations were found in this study. Dashed arrows indicate multiple processes. CoA, Coenzyme A; HMG, hydroxymethylglutaryl.
Response to therapy in DSAP. A decrease in scaling was noted as early as week 1 in FP100-1. After 4 weeks of therapy, a marked decrease in erythema, scaling, and size of visible lesions was noted (Fig 2). After this dramatic result, we sought to address the possibility that skin lesions in porokeratosis derive primarily from cholesterol depletion but found no clinical improvement after 4 weeks of treatment with twice daily application of 2% cholesterol in the same vehicle as our compounded cholesterol/lovastatin on the right upper limb. After 3 months of combined cholesterol/lovastatin therapy, only small erythematous macules were observed in treated areas (Fig 2).

Response to therapy in PPPD. FP100-6 was treated for 6 weeks, resulting in a prominent decrease of scaling and a moderate decrease of erythema (Fig 3). FP100-9 was treated for 8 weeks, which resulted in a prominent decrease of scaling and a moderate decrease in erythema (Fig 3). In both patients, improvement in scaling was noticed within 4 weeks of therapy, and there was no change in number and size of lesions.

Response to therapy in LP. A remarkable decrease in scale was noted in both LP patients 3-4 weeks after initiation of therapy. LP-1 was noted to have a pronounced decrease in erythema and thickness after 5 weeks of therapy (Fig 4). LP-2 had a decrease in thickness and scaling within 4 weeks of therapy; after 3 months of treatment, he displayed a moderate decrease in thickness and residual scale over the thicker component of his linear plaque (Fig 4).

Adverse events. All patients tolerated the therapy with no adverse events. Redness, irritation, pruritus, and allergic contact dermatitis at treatment sites were not reported. FP100-6 used a smaller treatment area than other patients because of concerns for systemic absorption of lovastatin while breastfeeding.

DISCUSSION

The advent of next-generation sequencing has enabled discovery of the genetic basis of skin disorders and furthered our understanding of their pathogenesis, introducing the opportunity for pathogenesis-directed treatment modalities. Here, we describe a pathogenesis-directed therapy for porokeratosis, targeting the mevalonate metabolic pathway in patients with known MVD or PMVK mutations. Most notable was the observation that, as has been demonstrated in other metabolic disorders, replenishment of a diminished end product of the mevalonate pathway alone had no treatment effect, but dual end-product
replenishment and toxic metabolite inhibition with a statin resulted in varying degrees of improvement in 3 variants of porokeratosis. Although further work is needed to definitively establish the exact mechanism of this treatment, the efficacy of the dual treatment is likely attributable to the added effect of inhibition of toxic metabolite accumulation.21

Although near-complete resolution was observed in our patient with thin red DSAP plaques after
topical cholesterol/lovastatin treatment, the thick or atrophic brown-purple plaques in LP and PPPD patients were noted to have a partial response after 5-8 weeks of therapy. Because the lesions of the included patients with LP and PPPD were thicker or more atrophic than the lesions of the patient with DSAP, we hypothesize that they did not achieve their maximal response and could continue to improve, as seen in CHILD syndrome with the same regimen.16 In addition, thicker lesions might achieve greater response when treated with a vehicle with greater bioavailability potential.22 Last, deficiency in mevalonate pathway end products other than cholesterol could contribute to the phenotype, and replenishment of these products could be needed to improve responses of the partially responding lesions.

The exact role of topical statin application in the treatment of porokeratosis remains to be fully elucidated. Of note, our hypothesis that bioactive precursors accumulate in keratinocytes and contribute to porokeratosis pathogenesis is supported by the lack of response to exclusive cholesterol application, but the exact toxic precursors and mechanism of destruction are still unknown.21 Mevalonate kinase deficiency is an autoinflammatory disorder with a spectrum of manifestations (eg, hyperimmunoglobulinemia D and periodic fever syndrome, mevalonic aciduria). Mevalonate kinase deficiency is caused by recessive or compound heterozygous MVK mutations. Although 1 study suggested that the inflammatory hyperresponsiveness of the disease appears to be caused by the lack of protein prenylation,23 more recent work has demonstrated that mevalonate accumulation contributes to disease pathogenesis by inducing innate immune cells via activation of insulin-like growth factor 1 receptor and mammalian target of rapamycin and subsequent histone modification in inflammatory pathways.24 In this study,24 a statin, which blocks mevalonate generation, prevented immune activation, and 6-fluoromevalonate, an MVD inhibitor, augmented the induction of proinflammatory cytokine production, indicating that the accumulation of a molecule upstream of 6-fluoromevalonate (mevalonate) plays a role in the induction of cytokine production, excluding a role for protein prenylation. Interestingly, patients with hyperimmunoglobulinemia D and periodic fever syndrome treated with statins showed a reduced excretion of mevalonate and a decreased number of febrile days, supporting the concept that lowering mevalonate levels is beneficial for disease activity.25,26 In contrast, patients with mevalonic aciduria (ie, a more severe presentation of mevalonate kinase deficiency) flared with lovastatin treatment.27 Keratinocytes also play a role in the innate immunity.28 Although this finding suggests that mevalonate accumulation might contribute to porokeratosis pathogenesis and other studies of disorders of postsqualene cholesterol synthesis have shown that toxic precursor sterols play a role in disease pathogenesis, further work is needed to clarify the role of mevalonate and other potential toxic metabolites in porokeratosis pathogenesis.

**Fig 4.** Linear porokeratosis. Clinical improvement of skin of patients LP1 and LP2 with topical application of cholesterol/lovastatin. LP, Linear porokeratosis.
We hypothesized that blockade of metabolite production alone with a statin would not be efficient and would result in adverse events on the basis of previous murine studies that demonstrated ichthyosiform changes with topical solvent-dispersed statin application, reflecting the key role of cholesterol in the epidermal barrier. Statin-induced cholesterol deficiency can led to decreased number and internal contents of epidermal lamellar bodies, as well as altered lamellar bilayer architecture, with no evidence of cytotoxicity. Decreased number of lamellar bodies and disrupted lamellar bilayer architecture have been demonstrated in keratinocytes beneath the cornoid lamella in porokeratosis, presumably reflecting the role of cholesterol deficiency in porokeratosis pathogenesis. We believe that monotherapy with topical statins should be considered for treatment of porokeratosis for a number of reasons. First, nonphysiologic (petrolatum) lipid application, which leads to the addition of lipids strictly to the stratum corneum, has been shown to improve the barrier more rapidly than solvent-dispersed physiologic lipids that normalize lamellar body contents and lamellar bilayer architecture. Second, in 1 report on CHILD syndrome, skin lesions responded to topical simvastatin monotherapy in an ointment base. In addition, the kinetics of the response to topical dual regimen versus monotherapy should be studied.

In summary, topical cholesterol/lovastatin is an effective pathogenesis-directed treatment for porokeratosis. Although our experience treating a small series of patients supports the use of topical cholesterol/lovastatin for porokeratosis treatment, larger randomized clinical trials will be necessary to systematically evaluate the efficacy and safety of this therapy. In vitro studies can further elucidate the importance of the depletion of other pathway end products in the pathogenesis of this condition. In the interim, considering that cholesterol and lovastatin have known safety profiles and are relatively inexpensive, the topical cholesterol/lovastatin regimen provides an effective and well-tolerated option for porokeratosis therapy, including cases with extensive skin involvement.

REFERENCES


