alopecia. Finally, patients with serine protease inhibitor Kazal type 5 (SPINK5) mutations reported alopecia, consistent with phenotypic characterizations of Netherton syndrome (Figure).6

Within the ABCA12 and TGM1 subgroups, severity of alopecia correlated positively with severity of ichthyosis. Thus, while severities did not appear to be associated in patients with ichthyosis overall, they may have been associated in patients with ABCA12 and TGM1 mutations.

Our study was limited by a small sample size and inability to control for age. Some experts report anecdotally that alopecia in this population improves or worsens. The population was composed of 8 genotypes, and larger studies focusing on single genotypes might bear different results. Nevertheless, the findings suggest that in patients with TGM1 and ABCA12 genotypes, alopecia may be more extensive in cases of severe skin disease.

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Topical Itraconazole for the Treatment of Basal Cell Carcinoma in Patients With Basal Cell Nevus Syndrome or High-Frequency Basal Cell Carcinomas: A Phase 2, Open-Label, Placebo-Controlled Trial

Nonsurgical therapies are needed for patients with multiple basal cell carcinomas (BCCs). Vismodegib reduces BCCs but causes severe adverse effects and cannot be formulated as a topical treatment.1-4 Oral itraconazole is a weaker hedgehog (HH) pathway inhibitor and has shown evidence of reduced BCCs in Ptch1+/− mice and in 1 phase 2 trial.3,5 However, the risks of long-term treatment with oral itraconazole include liver dysfunc-
tion and congestive heart failure. We developed a topical itraconazole gel at the maximum soluble concentration that showed high dermal concentrations. In mice, itraconazole, 0.7%, gel reduced BCCs, showed no skin irritation, and achieved less than 1/100th the plasma level compared with oral itraconazole.4 Thus, we initiated a phase 2 trial evaluating itraconazole, 0.7%, gel vs placebo gel in patients with multiple BCCs.

Methods | Six patients with basal cell nevus syndrome (BCNS) and 3 patients with high-frequency BCCs (HF-BCCs; defined as mean >3 BCCs annually) were enrolled at Stanford in this open-label, intrapatient trial from May 2016 to October 2017. This study was approved by the Stanford University institutional review board and patients provided written informed consent. Patients contributed 1 BCC tumor at baseline for \( \text{GLI1} \) messenger RNA (mRNA) measurements using quantitative reverse transcription polymerase chain reaction (RT-PCR; methods previously described),\(^{5}\) 1 or more tumors for treatment with placebo gel twice daily, and 2 or more tumors for treatment with itraconazole, 0.7%, gel twice daily for 4 to 12 weeks (Dow Labs; see the Trial Protocol in the Supplement). Inclusion criteria included age 18 years or older, 4 or more BCCs at baseline, and a negative urine pregnancy test. Exclusion criteria included a history of congestive heart failure and liver disease (more details available at NCT02735356). The primary outcome was reduction in \( \text{GLI1} \) mRNA levels determined by RT-PCR, and the secondary outcome was change in BCC tumor area. Data analysis was performed from February 2018 to December 2018.

Results | Of 15 patients screened, 9 were enrolled: 6 with BCNS (81 tumors) and 3 with HF-BCCs (33 tumors). Of 114 tumors, 42 were treated with placebo, 65 with topical itraconazole, and 7 BCCs were biopsied for baseline \( \text{GLI1} \) mRNA levels (Figure). Seven...
patients were male; the majority (10; 67%) were non-Hispanic white with mean age 53 years. Six of the 9 participants who enrolled for 4 weeks continued for 12 weeks. There was no difference in the mean percent change in GLII mRNA levels between itraconazole and placebo groups at 4 weeks (12% vs 19.0% from baseline; \( P = .20 \)). There was no statistically significant difference in the percent change in tumor area between itraconazole and placebo at 4 weeks (0.04% vs -10.9% from baseline; \( P = .40 \)) and 12 weeks (8.9% vs 26.5%; \( P = .40 \)). In post hoc analysis, the itraconazole group showed reduced BCC tumor area in the subgroup of BCCs located on the back; however, given multiple testing for different anatomic locations, this difference was ultimately not statistically significant. Using liquid chromatography–mass spectrometry, intratumor itraconazole concentration was 133 μg/g of skin at 4 weeks and 96 μg/g at 12 weeks. There was no association between change in BCC tumor area and GLII mRNA levels. Other major metabolites such as hydroxyitraconazole were not measured given their weaker half maximal inhibitory concentrations (IC50).

One patient had grade 1 liver function test abnormalities at weeks 4 and 12, but this patient had fatty liver disease. Plasma itraconazole levels were undetectable after 4 and 12 weeks, except for 1 patient with a plasma level of 4.12 ng/mL. Topical itraconazole caused only grade 1 to 2 adverse effects: accept for 1 patient with a plasma level of 4.12 ng/mL. Topical itraconazole caused only grade 1 to 2 adverse effects: application site reaction (n = 4), pruritus (n = 4), lesion pain (n = 3), dysgeusia (n = 1), and xerosis (n = 1). These adverse effects resolved by the end of the study except in 2 patients who had persistent mild lesion pain, pruritus, and xerosis.

Discussion | Itraconazole, 0.7%, gel appears safe, is associated with intratumor drug concentrations after 4 weeks, and is not associated with systemic absorption. However, topical itraconazole failed to reduce GLII mRNA levels and tumor area. Topical and oral itraconazole are associated with BCC shrinkage in mice, but topical penetration in humans is more difficult owing to a thicker epidermis.

Conclusions | Itraconazole gel at the maximally soluble formulation of 0.7% did not reduce GLII mRNA levels and BCC tumor size. However, this study does not rule out whether other formulations of itraconazole at higher concentrations may be more effective.

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Distinct Histopathologic Patterns of Finger Eruptions in Dermatomyositis Based on Myositis-Specific Autoantibody Profiles

A number of myositis-specific autoantibodies have been identified in patients with dermatomyositis (DM), including anti-aminooacyl-transfer RNA synthetase (ARS), antimelanoma differentiation-associated protein 5 (MDA5), and antitryptase intermediary factor I (TIF1γ) antibodies, each of which is respectively associated with characteristic cutaneous manifestations.1,2 We analyzed the histologic findings of finger lesions based on these 3 myositis-specific autoantibodies.

Supplemental content

Distinct Histopathologic Patterns of Finger Eruptions in Dermatomyositis Based on Myositis-Specific Autoantibody Profiles

A number of myositis-specific autoantibodies have been identified in patients with dermatomyositis (DM), including anti-aminooacyl-transfer RNA synthetase (ARS), antimelanoma differentiation-associated protein 5 (MDA5), and antitryptase intermediary factor I (TIF1γ) antibodies, each of which is respectively associated with characteristic cutaneous manifestations.1,2 We analyzed the histologic findings of finger lesions based on these 3 myositis-specific autoantibodies.

Methods | This retrospective observational study was performed on patients with DM diagnosed with typical rash and the presence of anti-ARS, anti-MDA5, and TIF1γ antibodies detected using enzyme-linked immunosorbent assay kits (Medical and Biological Laboratories) in our dermatology departments from September 2007 to August 2018. We found 74 cases (30, 19, and 25 cases in the ARS, MDA5, and TIF1γ groups, respectively) where patients underwent skin biopsies of finger eruptions (eTable in the Supplement). The medical ethics review committee of each hospital exempted this study from ethical approval and waived the need for patient written informed consent because all data used were