The Safety and Efficacy of Pimecrolimus, 1%, Cream for the Treatment of Netherton Syndrome

Results From an Exploratory Study

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Background: Impaired skin integrity in patients with Netherton syndrome (NS) results in significant systemic absorption of topically applied medications. Some have advocated the administration of pimecrolimus, 1%, topical cream for the treatment of patients with NS. Insufficient data exist with regard to its safety, systemic absorption, and efficacy.

Observations: An exploratory study was conducted involving 3 children with NS who received twice-daily application of pimecrolimus, 1%, cream over 18 months. There were no notable abnormalities in hematologic or chemistry profiles. Blood levels of pimecrolimus ranged from 0.625 to 7.08 ng/mL, with peak levels reached during the first month in all 3 patients. Dramatic reductions were observed in the Netherton Area and Severity Assessment, Eczema Area and Severity Index, Investigator Global Evaluation of Disease, and pruritus scores compared with baseline levels.

Conclusions: Use of pimecrolimus, 1%, cream was well tolerated and demonstrated marked improvements in nearly all of the parameters evaluated. Patients treated with pimecrolimus responded rapidly, within the first month of treatment, and improvement persisted throughout the study period. In adult patients receiving oral pimecrolimus, blood levels as high as 54 ng/mL for 3 months have not shown clinically significant immunosuppression. Absorption of pimecrolimus, 1%, cream was detectable, but levels were much lower than expected even when applied to 50% of total body surface area. Larger studies are warranted to determine the safety and efficacy of pimecrolimus, 1%, cream in the treatment of NS.

Trial Registration: clinicaltrials.gov Identifier: NCT00208026

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METHODS

EXPERIMENTAL PROTOCOL

This was an open-label, single-arm study to investigate the safety profile of topical pimecro-
limus cream, 1% (Elidel; Novartis Pharmaceuticals Corp, East Hanover, New Jersey), in the treatment of the cutaneous manifestations associated with NS. The study was approved by the institutional review board of the Children’s Hospital of Philadelphia.6

Enrolled patients were treated with conventional dosing of commercially available pimecrolimus, 1%, cream used twice daily as needed applied to affected areas. Patients were asked to limit application to no more than 50% of their total body surface area. The percentage of body surface area affected, and the total dose of pimecrolimus applied, as measured in grams, were determined for all patients at each follow-up visit. Patients 1 and 2 treated their ILC, whereas patient 3 treated the erythrodermic skin changes associated with her NS.

At each visit, routine blood tests to assess electrolytes, fasting glucose, liver, renal, and hematopoietic functions was performed at the Children’s Hospital of Philadelphia. Blood samples for pharmacokinetic measurements of pimecrolimus were drawn 1.5 hours after medication was applied on the study day. These samples were then shipped frozen via overnight courier to the Novartis bioanalytics reference laboratory located in Rueil-Malmaison, France, and were subjected to a liquid chromatography/tandem mass spectrometry assay. The occurrence of adverse effects was evaluated by the use of standard questionnaires.

Measures of clinical improvement of the dermatitis were assessed using both physician-determined scoring systems and patient-based self-assessments. Physician-determined scores included the Eczema Area and Severity Index (EASI), the Netherton Area and Severity Assessment (NASA) (eTable, http://www.archdermatol.com), a standard investigator’s Global Evaluation of Disease (IGED), and transepidermal water loss (TEWL) measurements using the noninvasive Vapometer device (Delfin Technologies, Kuopio, Finland). Patient-based self-assessments included pruritus scores and the Children’s Dermatitis Quality of Life Index (CDQLI) used with the permission of M. Susan Lewis-Jones, FRCP, FRCPCH (Ninewells Hospital and Medical School, Dundee, Scotland), and Andrew Y. Finlay, MBBS, FRCP (Cardiff University School of Medicine, Cardiff, Wales).1,5

Phase 1 of the study consisted of a series of visits over a 3-month period: an initial screening visit, followed by visits on days 1, 8, 14, 28, 56, and 84.

Phase 2 of the study consisted of a 15-month extension period. Patients and their families who chose to continue therapy after the initial phase were offered the opportunity to continue on in phase 2, during which additional evaluations (identical to evaluation visits during phase 1) and monitoring were performed at the additional time points of 6 months, 12 months, and 18 months (as determined from the time of enrollment in the original study).

### STUDY PARTICIPANTS

Patients meeting the criteria for diagnosis of NS were enrolled over a period of 3 years, from September 2005 through March 2008. During this time, 1 set of twin girls 12 years of age, and 1 girl 7 years of age entered the study.

Enrolled patients all had normal laboratory values within 3 months prior to enrollment and provided signed written informed consent and assent. Patients of child-bearing age underwent pregnancy testing during the trial. Washout periods were required for those using systemic steroids (4 weeks), systemic tacrolimus (4 weeks), immunosuppressive therapy (4 weeks), phototherapy (4 weeks), inhibitors of Cytochrome P 3A4 450 (CYP3A4) isoenzyme (2 weeks), topical tacrolimus (2 weeks), or topical pimecrolimus (2 weeks). Other prior topical therapies were discontinued the day before the therapy with pimecrolimus was begun. Any patient with a history of immune compromise, malignant disease, lymphoproliferative disorder, hypersensitivity or adverse reactions to macrolides or calcineurin inhibitors, or active viral, fungal, or untreated bacterial infection were excluded from participation in the study.

### RESULTS

All 3 patients completed phase 1. The families of all 3 patients elected to continue into phase 2.

### USAGE

During the 18-month trial, use of pimecrolimus was documented on the basis of the weight of tubes used. Patient 1 used 2045 g, patient 2 used 1167 g, and patient 3 used 5426 g, yielding a mean daily usage of 3.9 g/d, 2.2 g/d, and 9.7 g/d, respectively.

### SAFETY

During the 18-month observation period, a mild eosinophilia was noted at baseline and intermittently throughout the study in all 3 patients. A mild transaminitis arose in patient 1 in conjunction with a viral illness. Otherwise, no clinically significant abnormalities were observed in complete blood cell counts, hepatic function testing, electrolytes, blood urea nitrogen, or glucose monitoring. Peak levels of blood pimecrolimus ranged from 0.625 to 7.08 ng/mL (Table) with maximal levels reached during the first month of treatment in all 3 patients (Figure 1). Patients 1 and 2 had predominantly cutaneous findings of ILC without erythroderma and demonstrated lower blood pimecrolimus levels. The higher blood levels in patient 3 were seen in association with erythrodermic skin findings.

### EFFICACY

Baseline scores for EASI and NASA (a Netherton-specific modification of the EASI score that substitutes scaling for excoriation; see the eAppendix for details) were determined and compared with values obtained during treatment. Peak reductions from NASA baselines ranged from 54.1% to 91.7% and were reached 350 to 520 days into the study (Figure 2). Comparable findings were observed in EASI scores with maximal reductions of 62.3%
to 92.4% from baseline, reached 84 to 561 days after the start of the study (Figure 3). Notable and rapid improvement in scores were seen with both NASA and EASI as early as 1 week into therapy (Figure 2 and Figure 3).

Similar improvements in Investigator Global Evaluation of Disease, which was graded on a 5-point, 0 to 4 scale (see the eAppendix). A peak reduction of IGED scores of 55% to 75% was evident after 28 to 84 days. Scores for the CDQLI (Figure 4) were likewise observed, with patients describing improvements transitioning from moderate disease states to feeling essentially normal (total CDQLI scores of 0 and 1) and were manifest by 2 months into therapy with some maintaining notably improved quality-of-life measures well to the end of the study period (Figure 4). All 3 patients experienced complete subjective resolution of their pruritus at some point during the treatment period. In fact, most of the improvement occurred within 1 week of starting therapy.

Although all 3 patients showed marked improvement in NASA, EASI, IGED, and CDQLI scores, statistically significant differences between baseline measurements and final measurements at the level of P = .05 is not possible with such a small number of patients. Nevertheless, all of these measures showed striking improvement in all of the patients (Figure 5 and Figure 6).

Interestingly, no consistent trends were noted in measurements of transepidermal water loss among patients in this study. The 2 older patients with predominantly ILC saw increases in TEWL as they clinically improved, but the device began malfunctioning at the 6-month visit and, unbeknownst to us at the time, required calibration. As a result, values obtained from that point on for patients 1 and 2 as well as all values for patient 3 were not counted. It was interesting to note that although the values for the younger patient (patient 3) could not be considered entirely valid, a trend was observed in which the more erythrodermic findings were associated with decreases in TEWL in association with improvements in clinical findings.

In patients with NS, the lack of appropriate protease inhibition within the epidermis results in impaired barrier function that can lead to increased TEWL, a predisposition to skin infection, as well as a marked permeability to topically applied agents. Hydrocortisone acetate, 1%, topical ointment, a low-potency topical corticosteroid, used...
over large body surface areas over a period of 1 year in an 11-year-old boy with NS resulted in Cushing syndrome. Experience with topical tacrolimus, 0.1%, ointment for patients with NS, for example, has shown both remarkable efficacy as well as striking systemic absorption of the drug in this patient population. Even when diluted to concentrations of 0.005%, 0.0075%, and 0.01% and used over limited body surface areas, topical tacrolimus ointment applied to the skin in patients with NS has demonstrated low but detectable systemic absorption.

Pimecrolimus is an anti-inflammatory ascomycin macrolactam derivative that has demonstrated efficacy in the treatment of inflammatory skin disorders such as atopic dermatitis and contact dermatitis. The experience of using topical pimecrolimus, 1%, cream in patients with NS has been documented in case reports that have described 7 patients with evidence of both clinical efficacy and good clinical tolerability. In contrast to tacrolimus, measurement of pimecrolimus blood levels is not commercially available and currently can only be obtained through its manufacturer, Novartis.

There is a lack of sufficiently safe and effective options for treating the cutaneous manifestations of disease in children with NS. Use of pimecrolimus, 1%, cream was well tolerated and demonstrated clinically and statistically significant improvements in nearly all of the physician-rated and subject-rated parameters evaluated, including EASI, NASA, IGED, pruritus scores, and CDQLI. Patients treated with pimecrolimus responded rapidly,
with subjective improvements occurring sooner than those rated by clinical observers. Itching responded most dramatically to treatment, within 1 week of starting therapy, whereas the improvements in cutaneous manifestations took slightly longer to manifest. Reductions in disease severity were clinically significant within the first month, and these improvements in clinical parameters persisted throughout the 18-month period of the study. Clinically significant tachyphylaxis was not observed during the study period.

The original study had been designed to evaluate patients over a 3-month period. However, owing to the notable clinical improvements observed, the patients and their families requested that they continue treatment with pimecrolimus. In an effort to provide ongoing monitoring for these families, an amendment to the original study was submitted to the institutional review board at the Children’s Hospital of Philadelphia, and the protocol was approved for a 15-month extension for families wishing to extend their trial.

The use of topical tacrolimus has been associated with significant systemic absorption in children with NS.12,13 The absorption of pimecrolimus through the skin in patients with NS is, by contrast, considerably diminished, as demonstrated by the relatively low blood levels observed in these 3 patients. It seems that these observations would further validate previous studies that have suggested that the percutaneous absorption of pimecrolimus is significantly less than that seen with tacrolimus and corticosteroid preparations in the context of inflamed skin.2,14

In adult patients with psoriasis and atopic dermatitis receiving oral pimecrolimus, blood levels as high as 54 ng/mL for 3 months have not demonstrated apparent immunosuppression.15,16 In patients with NS, absorption of pimecrolimus, 1%, cream was detectable, but levels were much lower than expected even when applied to 50% of total body surface area for up to 18 months. No clinical evidence of immune suppression—increased rate of infections, opportunistic infections, hematologic abnormalities (eg, leukopenia, lymphopenia, or neutropenia)—were noted.

The biological meaning of detectable pimecrolimus blood levels remains unknown. Earlier animal studies indicated that exposures to high doses of calcineurin inhibitors such as tacrolimus and pimecrolimus were associated in a dose-dependent manner with the development of malignant skin diseases and lymphoma. Based in part on these data, the US Food and Drug Administration instituted a series of public health advisories, medication guides, and boxed warnings for both drugs to increase consumer awareness about this potential risk.16,17 At the same time, more recent studies suggest alternative conclusions. A case-control study involving 5000 adults with dermatitis administered by questionnaire was designed to detect a 2-fold increased risk for nonmelanoma skin cancer in patients using topical calcineurin inhibitors. However, the analysis indicated instead that there was a dose-dependent decrease in the odds ratio for nonmelanoma skin cancer (range, 0.41-0.69) associated with the use of these agents when adjustments were made for age, sex, previous nonmelanoma skin cancer, and history of atopic dermatitis.18 Another study investigated the possible association of topical immunosuppressants and lymphoma in a cohort of patients with atopic dermatitis using a nested case-control design and identified 294 cases of lymphoma among 293 253 patients in the PharMetrics database. Adjusted analyses indicated that the use of topical calcineurin inhibitors was not independently associated with lymphoma, whereas the severity of atopic dermatitis seemed to be the most statistically significant factor associated with an increased risk of lymphoma.20

A correlation might exist between elevated blood pimecrolimus levels and the degree of calcineurin inhibition in circulating lymphocytes, which would then function as a highly sensitive marker for immune suppression. An assay for lymphocyte calcineurin inhibition, however, has only recently become available through the Novartis bioanalytics reference laboratory (during the final 6 months of this study) and could therefore not be successfully incorporated into the study prior to study end. Future investigations establishing baseline controls for lymphocyte calcineurin inhibition and measurements in patients with NS might help answer the question of whether these levels of blood pimecrolimus translate into measurable immunosuppression at the level of the lymphocyte and provide a basis for investigating whether these findings might have clinical relevance.

Pimecrolimus, 1%, cream applied topically seems to moderate the skin findings of patients with ILC and erythroderma seen in patients with NS. Although it is difficult to generalize from a small number of patients, it seems that the use of pimecrolimus cream is associated with very low levels of systemic absorption (less with ILC, and more absorption with erythrodermic NS, although these findings might be in part confounded by the fact that patients with ILC typically used less daily medication on average than the patient treating her erythrodermic skin changes). Given the favorable safety and efficacy profile encountered in this exploratory pilot study, and because patients with NS who respond to therapy are likely to desire continuing pimecrolimus as ongoing chronic treatment, larger studies and greater clinical experience are warranted to determine the longer-term safety and efficacy of pimecrolimus, 1%, cream in the treatment of NS.

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Author Contributions: Dr Yan was the principal investigator for this study. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.


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Online-Only Material: An eAppendix and eTable are available at http://www.archdermatol.com.

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REFERENCES