Safety and Efficacy of Pimecrolimus in Atopic Dermatitis: A 5-Year Randomized Trial

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BACKGROUND AND OBJECTIVES: Atopic dermatitis (AD) primarily affects infants and young children. Although topical corticosteroids (TCSs) are often prescribed, noncorticosteroid treatments are needed because compliance with TCSs is poor due to concerns about their side effects. In this longest and largest intervention study ever conducted in infants with mild-to-moderate AD, pimecrolimus 1% cream (PIM) was compared with TCSs.

METHODS: A total of 2418 infants were enrolled in this 5-year open-label study. Infants were randomized to PIM (n=1205; with short-term TCSs for disease flares) or TCSs (n=1213). The primary objective was to compare safety; the secondary objective was to document PIM's long-term efficacy. Treatment success was defined as an Investigator's Global Assessment score of 0 (clear) or 1 (almost clear).

RESULTS: Both PIM and TCSs had a rapid onset of action with >50% of patients achieving treatment success by week 3. After 5 years, >85% and 95% of patients in each group achieved overall and facial treatment success, respectively. The PIM group required substantially fewer steroid days than the TCS group (7 vs 178). The profile and frequency of adverse events was similar in the 2 groups; in both groups, there was no evidence for impairment of humoral or cellular immunity.

CONCLUSIONS: Long-term management of mild-to-moderate AD in infants with PIM or TCSs was safe without any effect on the immune system. PIM was steroid-sparing. The data suggest PIM had similar efficacy to TCSs and support the use of PIM as a first-line treatment of mild-to-moderate AD in infants and children.

WHAT'S KNOWN ON THIS SUBJECT: Topical corticosteroids are often used to treat atopic dermatitis (AD) in infants, although compliance is poor due to concerns over side effects. Pimecrolimus was shown to be a safe and effective noncorticosteroid treatment of AD in infants in short-term studies.

WHAT THIS STUDY ADDS: The Petite Study shows that long-term management of mild-to-moderate AD in infants with pimecrolimus or topical corticosteroids was safe without any effect on the developing immune system. Pimecrolimus had similar efficacy to topical corticosteroids and a marked steroid-sparing effect.
Atopic dermatitis (AD) is a chronic inflammatory, relapsing, and pruritic skin disease that affects up to 25% of infants and has a substantial impact on the quality of life of both patients and their families.1–3 AD, together with food allergy, is thought to be the first step of the “atopic march,” in which allergen exposure of the skin can lead to the subsequent development of asthma and allergic rhinoconjunctivitis.4 Patients with AD often need frequent interventions for disease flares and sometimes long-term continuous therapy to suppress the inflammation of the skin. Topical corticosteroids (TCSs) are commonly used as first-line treatment of AD,5 although their long-term safety and efficacy have not been investigated in infants. More than 80% of patients or caregivers have concerns about prescribed TCSs, and approximately one-third of AD patients are noncompliant with TCSs because of factors such as their potential side effects,6 which highlights the need for alternative noncorticosteroid treatments.

Pimecrolimus cream 1% (PIM) is a topical calcineurin inhibitor that selectively suppresses activation of T cells and mast cells.7,8 PIM is often recommended by prescribers as first-line AD therapy for sensitive skin areas because it causes neither epidermal barrier function impairment nor skin atrophy.5,9,10 Up to 2 years of PIM is effective and well tolerated in infants and children with mild-to-moderate AD.11–16 The Petite Study sought to compare the safety and efficacy of PIM and TCSs for the management of mild-to-moderate infantile AD during 5 years of evaluation. The safety analysis included several assessments of immune function, given concerns that PIM-mediated immunomodulation could affect the developing immune system. The study used a unique real-world design in which TCSs were used according to their label and in which the caregivers of infants randomized to treatment with PIM had ready access to short-term TCSs as rescue medication if AD flares could not be controlled with PIM.

METHODS

Patient Population

Patients were enrolled into the study between April 2004 and October 2005. Eligible infants were aged ≥3 to <12 months, and AD was diagnosed according to the criteria of Seymour et al17 (because these criteria were developed for patients aged ≤2 years) with disease affecting ≥5% of the total body surface area (TBSA). Patients had an Investigator’s Global Assessment (IGA) score of 2 or 3 (scale range: 0–5; Supplemental Table 3), indicating mild-to-moderate disease.

Patients were excluded if they used systemic corticosteroids, immunosuppressants, cytostatic drugs, or phototherapy within 4 weeks of the first application of study medication, topical tacrolimus ointment or PIM within 2 weeks, and topical therapy for AD such as TCSs within 3 days. Also excluded were immunocompromised patients and those with a history of malignant disease, active acute viral skin infection, or clinically infected AD.

Study Design

The primary objective of this 5-year, multicenter, open-label, randomized, parallel group study (www.clinicaltrials.gov identifier NCT00120523) was to compare the safety of PIM and TCSs over the first 5 to 6 years of life by assessing adverse events (AEs), and the effects of treatments on the developing immune system and growth rate. The secondary objective was to examine the long-term efficacy of PIM.

Patients were randomized in a 1:1 ratio to either PIM 1% cream or TCS (low potency, eg, hydrocortisone 1%; or medium potency, eg, hydrocortisone butyrate 0.1%; cream/ointment used according to the country’s label with potency selected by the investigator), and randomization was stratified by center and age group (3–6 and >6–<12 months) using a validated Interactive Voice Response System. Details of the treatment plan are shown in Supplemental Table 4. Study medication was started immediately after randomization and continued until complete AD clearance or for as long as allowed by the label of the specific TCS. Medication was reinitiated at the occurrence of first signs and symptoms of AD flares. Investigators explained to caregivers of patients in both groups what constituted disease worsening and, to those in the PIM group, when to stop PIM and start using a TCS, that is, as a rescue medication for an exacerbation not controlled by PIM.

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Independent Ethics Committee or Institutional Review Board for each center. Caregivers provided written informed consent for infants’ participation in the study.

Efficacy and Safety Assessments

Efficacy was evaluated by investigators during clinic visits using the IGA (range 0–5) for the whole body with a score of 0 (clear) or 1 (almost clear) indicating treatment success, and the TBSA affected by inflammation. Special consideration was given to facial AD. These straightforward and non–time-consuming efficacy assessments were considered suitable for this large-scale clinical study.

All AEs were coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (version 13.1). (AEs of primary clinical interest as defined by the US Food and Drug Administration are identified in Fig 3 later in the article.) Growth rate was assessed by measuring height and weight at each occasion.
visit. AEs recorded for the PIM group may have occurred either during treatment with PIM or with TCS for a flare.

Immunology assessments included antibody titers to common vaccine antigens, evaluations of humoral and cellular immune responses, and T-cell function tests (see Supplemental Information).

**Statistical Analysis**

The safety and intent-to-treat populations included all randomized patients who received at least 1 application of study medication. Assuming a 40% dropout rate, a sample size of 2350 infants was considered to provide ≥80% or ≥90% power to determine whether the AE incidence rates under varying scenarios were equivalent in the treatment groups. This calculation assumed that the expected true difference was zero and used the upper bound of the 97.5% confidence interval as the upper equivalence limit. The immunology test population comprised all patients who had at least 1 immune system function assessment and was to include ~350 patients per treatment group. All significance testing was 2-sided at the 5% significance level.

The primary safety analyses were performed on AEs of primary clinical interest and those with a crude incidence of ≥5% in either treatment group. These included Kaplan-Meier analysis of time to first occurrence of the AE. AE profiles for the treatment groups were compared using the log-rank test. Additionally, AE counts in specific time intervals were analyzed using a Generalized Estimating Equations Poisson regression model with baseline age and IGA, time, and treatment as explanatory variables. The crude incidence rate and relative risk based on the incidence density rate were also calculated for the AEs of primary clinical interest. The incidence density rate per 1000 person-months (ie, sum of study durations in months across all patients in a treatment group).

The presence or absence of antibody titers against vaccines was analyzed using a logistic regression model with time of vaccination, age group, and treatment as explanatory variables. Treatment group differences in percentage change from baseline to each postbaseline time point in T and B lymphocytes, and immunoglobulins (Ig) were evaluated together with 95% confidence intervals calculated under the assumption of equal variances using pooled variance. *Candida* skin and T-cell function tests were reported with descriptive statistics.

Analysis of growth rate was done by calculating the percentile and z score for height and weight for each patient at time points defined in the protocol using standard growth curves for the US population. The mean and change from baseline for observed height and weight as well as percentiles were summarized by treatment group at each time point. A mixed model analysis of the growth curve data were also performed to examine developmental trajectories with height and weight z scores as the response variable and time and treatment as explanatory variables. No statistical testing of efficacy endpoints was performed.

**RESULTS**

**Patients**

Overall, 2439 infants were randomized into the study, 2418 of whom received at least 1 dose of study drug (PIM, 1205; TCS, 1213) and were included in the efficacy and safety evaluations. A similar proportion of patients in each group completed the treatment period: PIM, 69.4%; TCS, 72.1% (Fig 1).

The baseline demographic and clinical characteristics of the treatment...
groups were similar (Table 1). On inclusion, the majority of patients were 6 to 12 months old. Although the study was designed to enroll infants aged 3 to <12 months, 15 patients older than 12 months (14 patients <12.5 months old; 1 patient 12.8 months) were entered and included in the analyses. The 383 PIM- and 391 TCS-treated patients in the immunology test population had similar baseline characteristics to the overall population (data not shown).

**Efficacy**

Both PIM and TCSs had a rapid onset of action (Fig 2). More than 50% of infants in both groups achieved overall (PIM, 52.6%; TCS, 50.5%) or facial IGA (PIM, 61.0%; TCS, 61.8%) treatment success (ie, IGA <3 by week 3). The median TBSA affected by AD decreased from 16% at baseline to <5% by week 3 (PIM, 3.8%; TCS, 4.0%; Fig 2). At the end of the 5-year study, >85% (PIM, 88.7%; TCS, 92.3%) and 95% (PIM, 96.6%; TCS, 97.2%) of patients achieved overall and facial IGA treatment success, respectively (Fig 2A and 2B). Similarly, the median TBSA affected by AD decreased to 0% after 1.5 years of “as-needed” treatment and was maintained at this level for the rest of the study (Fig 2C).

### TCS and Pimecrolimus Exposure

PIM was associated with a steroid-sparing effect. Thirty-six percent of patients in the PIM group did not use any TCSs. Overall, the patients in the PIM group used TCSs for a median of only 7 days (Q1: 0, Q3: 49 days) compared with 178 days (Q1: 77, Q3: 396 days) in the TCS group over the 5-year study period (Supplemental Fig 5). Patients in the PIM group used PIM for a median of 224.5 days (Q1: 90, Q3: 452 days).

### Immune System

Infants treated with PIM or TCSs developed similar and normal antibody titers to common vaccine antigens (Table 2). To evaluate the magnitude of the antibody response of infants being treated with study drug after immunization, the response to *Haemophilus influenzae* type b vaccine was assessed by measuring antibody titers before the third dose of primary vaccination and 30 days after vaccination, the response to *Haemophilus influenzae* type b vaccine was assessed by measuring antibody titers before the third dose of primary vaccination and 30 days.

### Safety

The frequency of the most common AEs was similar in both treatment groups (Supplemental Table 5). There were few discontinuations due to AEs (PIM, 0.6% [most common: application site reactions, 3 patients]; TCSs, 1.0% [most common: telangiectasia, 2 patients]). There was no difference in growth rate between the groups or in the Kaplan-Meier adjusted incidence of frequent AEs (≥5%) or AEs of primary clinical interest, such as bacterial or viral infections. Analysis of event counts for frequent AEs using the repeated Poisson regression model showed that patients in the PIM group experienced more AEs of bronchitis (P = .02), infected eczema (P < .001), impetigo (P = .045), and nasopharyngitis (P = .04). During the first 6 weeks and the entire study, the crude incidence and incidence density rate for the AEs of primary clinical interest were similar (Fig 3).

There were no differences in the Kaplan-Meier analysis of the time to first occurrence of these AEs.

Two deaths were reported in the TCS group, but considered unrelated to study medication (drowning, acute lymphocytic leukemia). The overall incidence of SAEs (PIM, 20.5%; TCS, 17.3%) and serious infections and infestations (13.0% vs 12.4%) were similar in the 2 groups. Two malignancies occurred in the TCS group (acute lymphocytic leukemia, ependymoma), and 1 benign tumor was reported in the PIM group (pilomatrixoma).

### Table 1 Patient Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PIM % (n = 1205)</th>
<th>TCS % (n = 1213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.1 (2.7)</td>
<td>7.1 (2.7)</td>
</tr>
<tr>
<td>&lt;3, n (%)</td>
<td>4 (0.3)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>3–6, n (%)</td>
<td>500 (41.5)</td>
<td>485 (40.0)</td>
</tr>
<tr>
<td>&gt;6–&lt;12, n (%)</td>
<td>684 (57.6)</td>
<td>713 (58.8)</td>
</tr>
<tr>
<td>≥12, n (%)</td>
<td>7 (0.6)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>744 (61.7)</td>
<td>742 (61.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>736 (61.1)</td>
<td>713 (58.8)</td>
</tr>
<tr>
<td>Black</td>
<td>66 (5.5)</td>
<td>80 (6.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>119 (9.9)</td>
<td>118 (9.7)</td>
</tr>
<tr>
<td>Other</td>
<td>284 (23.6)</td>
<td>302 (24.9)</td>
</tr>
<tr>
<td>TBSA affected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.1 (16.5)</td>
<td>21.3 (17.2)</td>
</tr>
<tr>
<td>&lt;15%, n (%)</td>
<td>568 (47.1)</td>
<td>575 (47.4)</td>
</tr>
<tr>
<td>15–&lt;30%, n (%)</td>
<td>378 (31.4)</td>
<td>367 (30.5)</td>
</tr>
<tr>
<td>≥30%, n (%)</td>
<td>259 (21.5)</td>
<td>271 (22.3)</td>
</tr>
<tr>
<td>IGA, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2, Mild disease</td>
<td>570 (47.3)</td>
<td>558 (46.0)</td>
</tr>
<tr>
<td>3, Moderate disease</td>
<td>635 (52.7)</td>
<td>652 (53.0)</td>
</tr>
<tr>
<td>4, Severe disease</td>
<td>0</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>5, Very severe disease</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Facial IGA, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, Clear</td>
<td>71 (5.9)</td>
<td>74 (6.1)</td>
</tr>
<tr>
<td>1, Almost clear</td>
<td>88 (7.3)</td>
<td>84 (6.9)</td>
</tr>
<tr>
<td>2, Mild disease</td>
<td>497 (41.2)</td>
<td>501 (41.3)</td>
</tr>
<tr>
<td>3, Moderate disease</td>
<td>541 (44.9)</td>
<td>537 (44.3)</td>
</tr>
<tr>
<td>4, Severe disease</td>
<td>7 (0.6)</td>
<td>15 (1.2)</td>
</tr>
<tr>
<td>5, Very severe disease</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Not stated</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>
postimmunization in a subset of patients. In both groups, all patients but 1 were seropositive (Table 2).

The increase in Ig levels and the decrease in peripheral blood T and B lymphocytes from baseline to week 260 were similar in both groups (Fig 4, Supplemental Fig 6) and considered normal compared with historical controls (for example, see Supplemental Fig 7). The proportion of patients with positive Candida skin tests was similar between treatment groups (baseline: PIM, 14.0%; TCS, 9.2%; week 260: 15.3% vs 14.3%). T-cell function was assessed by ex vivo cytokine production in response to stimulation with anti-CD3 antibodies and tetanus antigen. Accordingly, the production of interleukin (IL)-2, IL-4, IL-10, and interferon-γ was comparable in the 2 treatment groups, indicating a similar non–antigen specific activation response and specific antigen response (Supplemental Fig 8).

DISCUSSION

We investigated the safety and efficacy of PIM and TCSs in the largest population of infants with AD and for the longest time period (ie, the first 5–6 years of life) ever studied. Infants aged ≥3 to <12 months were selected for inclusion so that the effects of treatment could be investigated from early infancy through early childhood. The efficacy results suggest that PIM has similar efficacy to TCSs in a real-world setting, which is noteworthy because PIM is not currently widely used as first-line therapy for AD, given the perception of lower efficacy than TCSs.19 Both treatments had a rapid onset of action (within 3 weeks). After 5 years of as-needed treatment, 88.7% PIM-treated and 92.3% TCS-treated infants had only minimal disease, which could reflect a progressive increase in treatment efficacy and/or the natural progression of AD, which tends to get milder as children get older. The rapid and continuous improvement in AD may decrease the substantial physical and emotional burden caused by this distressing skin condition.20 These findings confirm and extend those from previous shorter studies in infants and young children, which

FIGURE 2
Long-term efficacy of PIM compared with TCSs: A, overall; B, facial IGA treatment success (IGA ≤1); C, TBSA affected. IGA treatment success is defined as an IGA score of 0 (clear) or 1 (almost clear).
showed that PIM leads to rapid relief of pruritus, prevention of progression to major flares, and increases in the number of disease-free days.\textsuperscript{11,12,21,22} Treatment with PIM resulted in a substantial corticosteroid-sparing effect, with 36% of children not requiring any TCSs over the 5-year study. Patients in the PIM group used TCSs for a median of only 7 days. The markedly decreased need for TCSs is important because it

FIGURE 3
Crude incidence and relative risk for AEs of primary clinical interest during (A) 6 weeks and (B) entire treatment period. Incidence density ratio was calculated as 1000 \times \frac{\text{total number of events}}{\text{total monitoring time in months}}. CI, confidence interval.
indicates that AD patients can be effectively treated with a noncorticosteroid alternative. Up to one-third of patients are not compliant with TCS treatment because of corticophobia, resulting from factors such as fear of their potential side effects.6,23–25 The steroid-sparing effect of PIM may help to improve treatment compliance, although this was not specifically assessed in the Petite Study.

In this 5-year study, there were no safety concerns with real-life use of PIM or TCSs. Overall, the type and frequency of AEs including infections were as expected for this patient population.26,27 There were no cases of T-cell lymphoma or skin malignancies with PIM during the study, in agreement with the findings of several long-term epidemiologic studies.28,29

There was an overall trend toward PIM being associated with a lower risk of rhinorrhea, wheezing, viral rash and lower respiratory tract infection over the entire treatment period (Fig 3). However, the incidence of some mild infections (bronchitis, impetigo, nasopharyngitis, infected eczema) was significantly higher with PIM than with TCSs. In contrast, a randomized double-blind study in adults reported a higher incidence of infections with TCSs.30 The differences in AE incidence between groups were only 2% to 4%, and the analyses were not adjusted for the multiplicity of comparisons.

### Table 2: Patients With Positive Antibody Titers

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>PIM 1% (n = 383)</th>
<th>TCS (n = 391)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td>164/180 (81.1)</td>
<td>169/190 (88.9)</td>
<td>0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>63/192 (34.6)</td>
<td>73/191 (38.2)</td>
<td>1.2 (0.9–1.6)</td>
</tr>
<tr>
<td>Measles</td>
<td>180/182 (98.9)</td>
<td>181/188 (96.3)</td>
<td>0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>Varicella</td>
<td>27/31 (87.1)</td>
<td>37/44 (84.1)</td>
<td>2.2 (1.0–4.7)</td>
</tr>
<tr>
<td>Hibc</td>
<td>26/27 (96.5)</td>
<td>30/31 (96.8)</td>
<td>0.9 (0.1–14.6)</td>
</tr>
</tbody>
</table>

CI, confidence interval; Hib, Haemophilus influenzae type b; n/N, number of patients with positive antibody titers / total number of patients with antibody titer measurements; OR, odds ratio.

* At week 260 for tetanus, hepatitis B, measles, varicella; 50 d postimmunization and before third dose for Hib.
* Only assessed for patients from the United States (PIM 1%, n = 104; TCS, n = 108).
* Only assessed in subset of patients from the United States and Canada.

**Figure 4**

Ig levels over time: A, IgA; B, IgE; C, IgG; and D, IgM.
Therefore, the clinical significance of the observed small differences in the incidence of 4 specific AEs needs to be interpreted with caution.

The immunologic investigations in this study represent the most comprehensive assessment ever performed of the impact of real-life AD treatment on the maturation of the immune system in a large international population of infants with AD during the first 5 to 6 years of life. Our study did not include a placebo arm for ethical reasons; however, the increase in Ig levels and decrease in circulating T and B lymphocytes were similar in both groups and consistent with the normal maturation of the systemic immune system in healthy children.\(^31\)--\(^36\) Previous studies have shown that IgG and IgA levels progressively rise during the first years of life in healthy children. IgE also rises, but to a lesser extent, and the levels of IgM plateau before those of the other Ig categories, in agreement with our findings.\(^31\)--\(^34\)

Also similar to our observations, other studies have demonstrated that T and B lymphocyte counts peak in the first 1 to 2 years of life, followed by a slow decline to adult levels over time.\(^35,36\) The postvaccination antibody titers showed that most patients developed a normal immune response to childhood vaccinations, and the response was similar in the 2 treatment groups. The current immunologic data confirm previous investigations demonstrating that up to 2 years of PIM treatment in infants did not result in an increased rate of systemic or skin infections and development of immune responses after vaccination were normal.\(^11,12,16,21,37\) These results provide important real-world data supporting the safety of PIM in infants and young children with a developing immune system. The lack of systemic immunosuppression is likely due to the minimal systemic drug exposure in both infants and children.\(^38,39\)

**CONCLUSIONS**

The Petite Study begins to address recommendations from regulatory agencies and The Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology that more studies are needed to address questions about the efficacy and safety of topical immunosuppressive medications specifically in pediatric populations with AD.\(^40\) The results of the Petite Study show for the first time that as-needed first-line treatment with PIM or TCSs has no safety concerns and no impact on the maturation of the developing immune system. The data suggest that PIM had similar efficacy to TCS and PIM was associated with a substantial corticosteroid-sparing effect. The study provides real-world data for the use of PIM as a first-line treatment of mild-to-moderate AD in infants and children.

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Dr Sigurgeirsson was the principal investigator for this study and as such approved the study report and vouches for the data; he contributed to the design and conduct of the study, collection of data, analysis and interpretation of the results, writing and critical review of the manuscript; Drs Bozanski, Todd, Schuttelaar, Zhu, Qaqundah, Kristjansson contributed to the acquisition of data for the study and critically reviewed the manuscript; Drs Vertruyen, Schauer contributed to the acquisition of data for the study and drafting the manuscript and critically revising its content; Drs Poulin and Nieto contributed to the acquisition of data for the study, analyzed and interpreted the results, and critically revised the manuscript; Dr von Berg contributed to the acquisition of data for the study, was involved in the interpretation of the results, and critically revised the manuscript; Dr Boguniewicz contributed to acquisition of data for the study and provided critical input into the initial and revised manuscript; Dr Paller carried out the initial analyses, reviewed and revised the manuscript; Dr Dakovic contributed to the analysis of data and critically reviewed the manuscript; Drs Ring and Luger analyzed and interpreted the results and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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