REVIEW ARTICLE

Safety and Tolerability of 1% Pimecrolimus Cream Among Infants: Experience With 1133 Patients Treated for Up to 2 Years

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ABSTRACT

Pimecrolimus is a calcineurin inhibitor developed for the topical treatment of atopic dermatitis. During the clinical development of 1% pimecrolimus cream, 1133 patients 3 to 23 months of age with mild to severe atopic dermatitis were treated for up to 2 years. The objective of this review is to discuss the safety and tolerability of 1% pimecrolimus cream among infants, on the basis of the combined results from all studies (4 pharmacokinetic studies and 6 clinical trials) conducted among these patients. Pimecrolimus blood concentrations measured for 35 patients were consistently low (≤1 ng/mL in >80% of samples), irrespective of the disease severity and extent, and remained low during intermittent treatment for up to 1 year. The level of systemic exposure to pimecrolimus among infants was comparable to that observed for older pediatric patients enrolled in the same studies and treated in the same way with 1% pimecrolimus cream, which indicated that young pediatric patients are not at higher risk of significant percutaneous absorption of topically applied pimecrolimus, despite their large skin surface area/body mass ratio. The 6 clinical trials included a total of 1098 infants, who were treated for periods ranging from 4 weeks to 2 years. Most of these patients (60%) had moderate to severe disease at baseline. The most frequently reported adverse events were common childhood disorders such as nasopharyngitis, pyrexia, upper respiratory tract infections, ear infections, and bronchitis. During the double-blind (DB) studies or DB phases of studies, the incidence rates for the most frequently reported adverse events were similar for patients who received 1% pimecrolimus cream and patients who received the vehicle, except for the incidence of teething, which was higher among the pimecrolimus-treated infants (relative risk: 2.02; 95% confidence interval: 1.32–3.27). Treatment with 1% pimecrolimus cream was not associated with an increase in the overall incidence of nonskin infections, compared with the vehicle (relative risk: 1.015; 95% confidence interval: 0.88–1.18). The incidence density (ID) rates for total bacterial, fungal, parasitic, and viral skin infections during the DB studies or DB phases of

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Key Words
pimecrolimus, atopic dermatitis, safety, infants

Abbreviations
AD—atopic dermatitis
CI—confidence interval
DB—double-blind
ID—incidence density
LoQ—limit of quantification
OL—open-label
TBSA—total body surface area
TCS—topical corticosteroid

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studies were comparable for patients treated with 1% pimecrolimus cream and patients who received the vehicle. The ID rate of herpes simplex virus infections was 0.8 cases per 1000 patient-months of follow-up monitoring among patients treated with 1% pimecrolimus cream and 1.7 cases per 1000 patient-months of follow-up monitoring among patients who received the vehicle. Considering all 1098 infants treated with 1% pimecrolimus cream in DB trials and open-label studies, the ID rate of clinically diagnosed eczema herpeticum was 1.3 cases per 1000 patient-months of follow-up monitoring. Burning and erythema were the most frequently reported application site reactions, with ID rates of 2.0 and 1.2 cases per 1000 patient-months of follow-up monitoring, respectively. No sign of immunosuppression was found among infants treated intermittently with 1% pimecrolimus cream for up to 2 years; they demonstrated normal immune responses to vaccinations and did not show increases in the incidence of systemic infections or skin infections over time.

ATOPIC DERMATITIS (AD) is one of the most common skin disorders among young children.[1] Approximately 15% to 20% of infants in Western countries suffer from this disease, and the prevalence is increasing.[1–5] Intractable itching and related sleep loss account for much of the suffering experienced by affected infants.[6,7] AD also affects the appetite and mood of infants.[6] Its negative impact on quality of life extends to the patients' family,[6,7] often severely disrupting the lives of parents and influencing, with detrimental effects, the care of other, unaffected children.

Topical corticosteroids (TCSs) have been the most commonly used antiinflammatory drugs for treatment of AD. Although TCSs are undoubtedly effective in treating acute manifestations of the disease, their prolonged unrestricted use is limited by local and systemic side effects.[8–15] Systemic side effects occur as a result of the penetration of topically applied corticosteroids through the skin into the circulation (percutaneous absorption). The major risk factors for increased percutaneous absorption of TCSs are disease extent and patient age, with young pediatric patients being at the highest risk[13] because of their large skin surface area/body mass ratio.[14,15] The perceived risks of side effects from TCS use have generated concern, resulting in "corticosteroid phobia" and poor compliance with treatment, particularly in the pediatric population.[16–18]

One percent pimecrolimus cream (Elidel, SDZ ASM 981; Novartis Pharma AG, Basel, Switzerland) is a topical calcineurin inhibitor that blocks the transcription and release of inflammatory cytokines and mediators that are produced by T lymphocytes and mast cells and are involved in the pathogenesis of AD and other inflammatory skin disorders.[19,20] It does not interfere with the differentiation, maturation, and function of cells involved in immunosurveillance, specifically dendritic cells/Langerhans cells.[21–25] Pimecrolimus cream has demonstrated a much lower potential for percutaneous absorption than TCSs, because of its higher molecular weight and lipophilicity.[26,27] Unlike TCSs, it does not cause skin atrophy and does not affect the hypothalamic-pituitary-adrenal axis.[26,28]

Pimecrolimus cream was developed specifically for the treatment of inflammatory skin diseases, such as AD, allergic contact dermatitis, and chronic irritant hand dermatitis.[29–34] The development program for AD involved a large number of infants (defined as subjects <24 months of age) and children, in recognition of the fact that AD is primarily a pediatric disease. A total of 1133 infants (age: 3–23 months) with mild to severe AD were treated intermittently with 1% pimecrolimus cream for up to 2 years. The results of clinical studies in this population of patients[35–40] demonstrated that the use of 1% pimecrolimus cream induces rapid symptom relief, prevents progression to major flares, increases the number of disease-free days, improves the quality of life of patients and their parents, and is well tolerated. Some of the clinical studies also provided evidence that, at variance with TCSs, 1% pimecrolimus cream retains its clinical effectiveness when used for extended periods[35,38,39] and can be discontinued without any risk of disease rebound.[38]

The safety of any new drug is of paramount concern to clinicians and defines the relative value of a new, effective, therapeutic option. The major concern with the use of 1% pimecrolimus cream is the fact that calcineurin inhibitors have immunosuppressive properties when administered systemically at high doses, although the immunosuppressive effects of systemically administered pimecrolimus are lower than those demonstrated with other drugs of the same class.[21] Therefore, it is important to confirm the preclinical and clinical data[20,26,30–32] indicating that topical applications of pimecrolimus are associated with minimal systemic absorption and do not lead to adverse experiences attributable to its immunosuppressive potential. This issue should be addressed particularly among infants, because the risk of systemic absorption of topical drugs for these individuals is higher than that for older children and adults.[13–15] The objective of this review is to discuss the safety and tolerability of 1% pimecrolimus cream among infants with AD, on the basis of the combined data from 4 pharmacokinetic studies and 6 clinical trials conducted with 1133 patients.

SYSTEMIC EXPOSURE IN PHARMACOKINETIC STUDIES

An important safety aspect to be addressed in the development of a topical treatment for young children is systemic absorption of the drug. Toxicology studies conducted with pimecrolimus administered through the oral route to animals indicated that the potential target organs for toxicity were the kidney, the pancreas, and

the lymphoid tissue. Toxicity was observed only at oral doses of pimecrolimus associated with mean peak blood concentrations of >100 ng/mL.[41] No systemic toxicity could be achieved through the topical route with pimecrolimus cream among animals. Among human subjects, no manifestations of toxicity were observed among adult psoriatic patients treated with orally administered pimecrolimus for up to 12 weeks, at doses associated with mean peak blood concentrations of 54 ng/mL.[42–46]

Systemic exposure to pimecrolimus during treatment with 1% pimecrolimus cream was assessed in pharmacokinetic studies by measuring pimecrolimus blood concentrations at various times during the treatment period. A summary of the pharmacokinetic studies completed among pediatric patients with AD is reported in Table 1. In total, 58 pediatric patients (age: 3 months to 14 years) were included. As shown in pediatric and adult pharmacokinetic studies, blood concentrations after treatment with pimecrolimus cream are very low or undetectable.[30,43,44] Blood concentrations display similar low values 2, 4, 6, and 12 hours after application, with no peak. Concentration ranges are similar on days 4 and 22, which indicates no systemic accumulation of pimecrolimus after topical application.

Four pharmacokinetic studies (W206 cohort 2, 0301, 0301-E1, and 0304) included 35 infants (age: 3.4–22.7 months) with moderate to severe AD involving 10% to 92% of the total body surface area (TBSA) at baseline (Table 1). One percent pimecrolimus cream was applied twice daily to all areas affected by AD until complete clearance of skin lesions, and treatment was resumed after recurrence of signs or symptoms. Thirty infants were treated for 3 weeks and 5 (study 0301-E1) continued treatment for up to 1 year (Table 1). In the 3-week studies,[30,43,44] venous blood sampling for measurement of pimecrolimus blood concentrations was performed on day 4, before and at least 2 hours after the morning application of 1% pimecrolimus cream, and on the last day of the treatment period (day 22). For the 5 infants who were treated with 1% pimecrolimus cream for up to 1 year, blood sampling was also performed 2 hours after the morning application of the study drug at week 27 and at the end of the study. Pimecrolimus blood concentrations were determined either with a radioimmunoassay, with a limit of quantification (LoQ) of 0.5 ng/mL, or with liquid chromatography/tandem mass spectrometry, with a LoQ of 0.1 ng/mL, as described elsewhere.[43,44]

In study W206, cohort 2, 55% of the 21 blood samples contained pimecrolimus concentrations below the LoQ. The highest pimecrolimus blood concentration measured was 2 ng/mL, excluding a single isolated value of >50 ng/mL that was attributed to contamination of the blood sample with the cream during venipuncture (the patient had AD lesions treated with 1% pimecrolimus cream in the area of venipuncture). In study 0301, pimecrolimus blood concentrations measured 2 hours after the morning application of 1% pimecrolimus cream, on day 4 and day 22, ranged from 0.28 ng/mL to 2.6 ng/mL, apart from an isolated value of 36.6 ng/mL that was attributed to contamination of the blood sample with the cream during venipuncture. For the 5 infants who extended their treatment for up to 1 year (study 0301-E1), pimecrolimus blood concentrations measured 2 hours after the morning application of the cream at week 27 and at study completion (10 blood samples in total) ranged from below the LoQ (0.1 ng/mL) to 1.94 ng/mL.[45] In study 0304, 86% of the 100 blood samples collected contained pimecrolimus concentrations of ≤1 ng/mL. In 31% of these samples, pimecrolimus blood concentrations were below the LoQ of 0.1 ng/mL. The individual pimecrolimus blood concentrations ranged from below the LoQ to 2.26 ng/mL, with the exception of 2 isolated values of 8.67 ng/mL and 42.2 ng/mL that were attributable to blood sample contamination with the cream during venipuncture. Considering the data from all of the studies reported in Table 1 according to age group (infants 3–23 months of age and children >24 months of age), similar frequency distributions of pimecrolimus blood concentrations could be observed for infants and children (Fig 1). Therefore, with the same pimecrolimus treatment regimen, systemic exposure to the drug among pediatric patients is low, irrespective of age, and much lower than that observed with a TCS such as hydrocortisone.[13] In the 3-week pediatric studies,

TABLE 1 Summary of Pharmacokinetic Studies

Study	Duration	No. of Subjects	Age Range	% of TBSA Affected at Baseline	Assay LoQ, ng/mL	Pimecrolimus Concentration Range, ng/mL	Reference
W202	3 wk	10	14–52 mo	23–69	0.5[a]	<0.5–1.8	43
W206 cohort 1	3 wk	10	8–14 y	21–49.5	0.5[a]	<0.5–2.0	44
W206 cohort 2	3 wk	8	8–30 mo	28–80	0.5[a]	<0.5–2.0	44
0301	3 wk	8	4.9–11 mo	25–58	0.1[b]	<0.1–2.6	44
0301-E1	Up to 1 y	5		39–52	0.1[b]	<0.1–1.94	45
0304	3 wk	22	3.4–22.7 mo	10–92	0.1[b]	<0.1–2.26	30

[a] Measured with radioimmunoassay.
[b] Measured with liquid chromatography/tandem mass spectrometry.

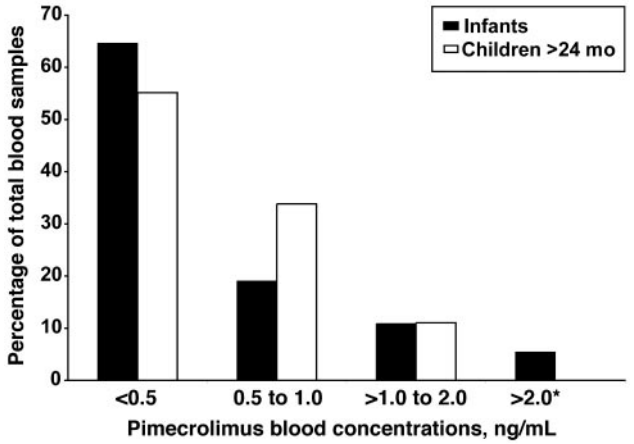

FIGURE 1
Frequency distribution of pimecrolimus blood concentrations among infants 3 to 23 months of age (147 blood samples for 35 patients) and children >24 months of age (136 blood samples for 23 patients). *Includes samples suspected of contamination with the cream during venipuncture.

pimecrolimus blood concentrations on day 22 were in the same range as those measured on day 4,[30,44] indicating that there was no evidence of drug accumulation during the treatment period. A linear regression analysis revealed a very small but statistically significant increase in the pimecrolimus blood concentrations with increasing proportions of TBSA affected by AD at baseline ($P = .028$).[44] However, the difference in mean pimecrolimus blood concentrations between a patient with 90% of the TBSA affected by AD and a patient with 10% of the TBSA affected by the disease was estimated to be 0.4 ng/mL.[30,44] Even for young patients with large proportions of TBSA affected by AD (70–92%), pimecrolimus blood concentrations were consistently low (<0.1–1.8 ng/mL).[30]

Overall, the results of pharmacokinetic studies among infants indicate that treatment with 1% pimecrolimus cream leads to minimal systemic exposure, even for patients with extensive disease, and that pimecrolimus blood concentrations remain low during treatment for up to 1 year. The highest concentration measured (2.6 ng/mL) was well below the mean peak concentration (54 ng/mL) detected among adult psoriatic patients treated for 28 days with 30 mg of pimecrolimus administered orally twice daily,[46] a dose that was well tolerated.[46] In line with these findings, no clinically relevant systemic adverse events were reported for the infants enrolled in the pharmacokinetic studies.[30,44]

CLINICAL STUDIES

Patients and Use of 1% Pimecrolimus Cream

Six double-blind (DB) or open-label (OL) studies evaluated the efficacy, safety, and tolerability of 1% pimecrolimus cream among infants with AD for periods ranging from 4 weeks to 2 years. The study design and patient characteristics are summarized in Table 2. Four of the 6 studies were either DB trials or trials involving a DB phase during which patients were treated intermittently with 1% pimecrolimus cream or the vehicle for periods ranging from 4 weeks (study DE-04) to 12 months (study 0315). In 2 of these trials (the 12-month study 0315 and the 6-month study US-04), patients in the pimecrolimus and vehicle groups were allowed to use TCSs if necessary to treat severe flares. A severe flare of AD was defined by an Investigator's Global Assessment score of at least 4, indicating severe erythema and/or severe infiltration/papulation of the skin. The TCSs used were medium-potency TCSs. In the 12-month study, one specific TCS was selected for use in each participating country. The corticosteroids used were 0.02% diflupredate cream, 0.1% hydrocortisone butyrate cream, 0.05% clobetasone butyrate cream, 0.02% triamcinolone acetonide cream, and 0.2% hydrocortisone valerate cream. In the 6-month study, 0.05% fluticasone propionate cream was used to treat severe flares. Concomitant use of 1% pimecrolimus cream and TCSs was allowed only in the 6-month study. Signifi-

TABLE 2 **Summary of Clinical Studies**

Study	Type	Duration	Age Range	AD Severity at Baseline	Treatment Arms	Reference
0315	DB study	12 mo	3–23 mo	Mild to severe	Pimecrolimus and TCSs if needed ($n = 204$) Vehicle and TCSs if needed ($n = 46$)	35, 39
0315-E1	OL phase	12 mo			Pimecrolimus and TCSs if needed ($n = 91$)	39
0316	DB phase	6 wk	3–23 mo	Mild to severe	Pimecrolimus ($n = 122$) Vehicle ($n = 63$)	37
	OL phase	20 wk			Pimecrolimus ($n = 185$)	37
C2405	OL study	6 mo	3 mo to 17 y	All severities	Pimecrolimus and TCSs if needed ($n = 947$)	
C2405-E1	OL phase	6 mo			Pimecrolimus and TCSs if needed ($n = 51$)	
US-04	DB study	6 mo	3 mo to 11 y	Mild to severe	Pimecrolimus and TCSs if needed ($n = 183$) Vehicle and TCS if needed ($n = 92$)	
DE-04	DB phase	4 wk	3–23 mo	Mild to severe	Pimecrolimus ($n = 128$) Vehicle ($n = 63$)	38
	OL phase	12 wk			Pimecrolimus ($n = 191$)	
C2420	OL study	3 mo	≥3 mo	Almost clear to severe	Pimecrolimus and TCSs if needed ($n = 2034$)	

cantly more patients in the pimecrolimus group did not use TCSs for 1 year, compared with patients in the control group, in the 12-month study (70% vs 39%). In the 12-month study, the proportion of study days with TCS treatment was 3.9% in the pimecrolimus group, compared with 9.6% in the control group. Similar results were obtained in the 6-month study. In all 6 studies, 1% pimecrolimus cream was applied twice daily to all areas of the skin affected by AD, from the first signs or symptoms of the disease until complete clearance, and treatment was resumed with recurrence of signs or symptoms, to prevent progression to severe flare.

In total, 1098 patients 3 to 23 months of age (530 of age <12 months) were included in the 6 studies; 637 (58.0%) were treated for at least 5 months, 466 (42.4%) for at least 6 months, 237 (21.6%) for at least 11 months, 190 (17.3%) for at least 1 year, 68 (6.2%) for at least 23 months, and 61 (5.6%) for at least 2 years. Considering the baseline characteristics of these 1098 patients, 7% had clear or almost clear disease according to the Investigator's Global Assessment,[30] 60% had moderate to very severe disease, and 33% had mild disease. For 609 of the 1098 patients, the proportion of TBSA affected by AD was assessed. The majority (65%) of patients had at least 15% of TBSA affected by the disease and 10% of patients had >60% of TBSA affected. The mean percentage of TBSA affected at baseline was 29% for 296 infants <12 months of age and 27% for 313 infants 12 to 23 months of age.

In the majority of these studies,[35–39] most of the full clinical benefit was observed within the first 1 week after the start of pimecrolimus treatment and maximal improvement was achieved within 3 months, after which the level of improvement was sustained. The use of 1% pimecrolimus cream decreased markedly between 3 and 9 months of treatment and remained low thereafter (Fig 2), with patients having on average ~44% to 57% treatment-free days from the ninth month onward. This indicated a substantial reduction in the patients' need for pharmacologic treatment as their disease improved and long-term control was achieved.

Combined Analysis of the Incidence of Adverse Events

In the 4 vehicle-controlled, DB studies reported in Table 2, the discontinuation rates ranged from 9.4% to 25% in the pimecrolimus groups and from 29% to 48% in the vehicle groups. The main reasons for discontinuation among infants treated with 1% pimecrolimus cream in clinical studies were unsatisfactory therapeutic effect (5.3%), loss of follow-up monitoring (3.4%), and withdrawal of consent (2.6%). Adverse events were the reason for discontinuation for 1.8% of patients. The main reason for the imbalance between treatment groups in terms of discontinuation rates was the higher incidence of premature discontinuations because of unsatisfactory therapeutic effect in the vehicle groups (range: 14–41%), in comparison with the pimecrolimus groups (range: 0–10%).

To correct for the differences between treatment groups in the length of time in the studies, which were attributable to that imbalance, a time-adjusted method was used to compare the incidence of adverse events in the DB phase of the controlled clinical trials. To account for the multiplicity of adverse events of the same type and to account for the time in studies, the total number of event occurrences (ie, events count) during the studies was analyzed by using the incidence density (ID) rate of all adverse events. The ID of an adverse event per 1000 patient-months was defined as the number of occurrences of that adverse event (k) divided by the total number of months patients were monitored in the studies, multiplied by 1000, according to the following formula: [(k/months in the study) × 1000]. Data from all infant studies were pooled for this analysis, to provide the largest available infant data set of adverse events. Along with the ID rates, relative risk estimates, corre-

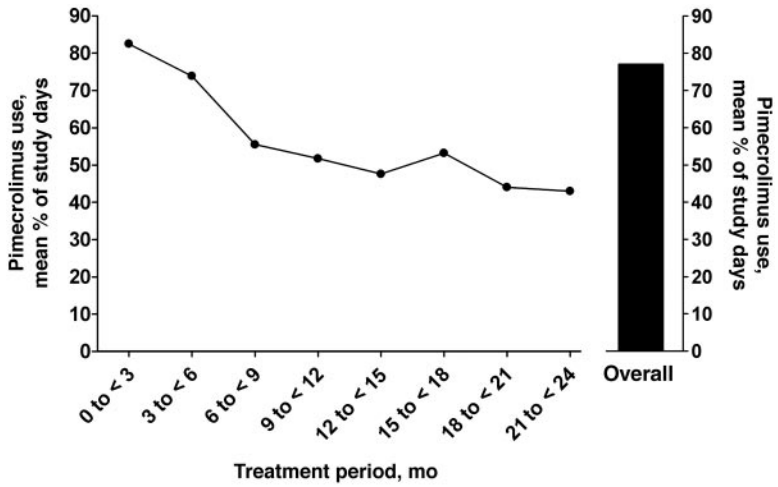

FIGURE 2
Summary of exposure to 1% pimecrolimus cream in the clinical studies listed in Table 2. Treatment days were defined as the number of days of pimecrolimus use from the start of treatment, regardless of dosing (once or twice daily). Calculated treatment days were expressed as percentages of days in the studies. Data represent the mean values per periods of 3 months (left) and the overall mean value (right).

sponding 95% confidence interval (CIs), and *P* values were calculated. The following 3 treatment groups were considered: (1) all patients who received 1% pimecrolimus cream during the DB studies or DB phases of studies (pimecrolimus DB); all patients included in the OL pimecrolimus studies or in the OL phases of DB studies were excluded from this group; (2) all patients who received the vehicle during the DB studies or DB phases (vehicle DB); and (3) all patients treated with 1% pimecrolimus cream; data from the DB phases were pooled with the data from all OL phases or studies (total pimecrolimus). The results of this analysis are reported below and were derived from unpublished reports on file at Novartis Pharma AG. These data should be interpreted by taking into account the fact that the number of patients in the pimecrolimus DB ($N = 495$) and total pimecrolimus ($N = 1098$) groups was much higher than the number of patients in the vehicle DB group ($N = 193$). Treatment periods were also longer for the total pimecrolimus group than for the pimecrolimus DB and vehicle DB groups, because of the inclusion of patients who received 1% pimecrolimus cream in all of the OL studies and OL phases (Table 2). Therefore, the chance of detecting infrequent adverse events was probably higher among patients treated with 1% pimecrolimus cream, particularly those in the total pimecrolimus group, than in patients who received the vehicle during the DB studies or phases.

Most Frequently Reported Adverse Events

The ID rates for adverse events that occurred for >1% of patients in any group are presented in Table 3. The majority of the most frequently reported adverse events were common childhood disorders such as nasopharyngitis, pyrexia, upper respiratory tract infections, ear infections, and bronchitis. The ID rates for all adverse events were similar in the pimecrolimus DB and vehicle DB groups, except for teething (discomfort experienced during the eruption of teeth through the gums), which was observed more frequently among patients treated with 1% pimecrolimus cream than among patients treated with the vehicle (relative risk: 2.02; 95% CI: 1.32–3.27; $P = .002$). In both groups, the severity of teething was mild to moderate. Only 1 patient discontinued use of the study drug because of teething in the pimecrolimus DB group. To the best of our knowledge, there is no clear scientific rationale to support an association between the use of topical pimecrolimus and teething. It could be a chance association or parents might have paid more attention to this symptom once the dermatitis had been cleared with 1% pimecrolimus cream.

Application site reactions, such as burning, erythema, and pruritus, occurred for <1% of the infants included in the 6 studies. Considering all patients treated with 1% pimecrolimus cream (total pimecrolimus), burning and erythema were the most frequently reported application

TABLE 3 **ID Rates (Cases per 1000 Patient-Months of Follow-Up Monitoring) for the Most Frequently Observed Adverse Events (>1% of Patients in Any Group), With Relative Risk, 95% CI, and *P* Values**

Adverse Events	Pimecrolimus DB[a] ID Rate, Cases per 1000 Patient-Months	Vehicle DB[b] ID Rate, Cases per 1000 Patient-Months	Relative Risk	95% CI	*P*	Total Pimecrolimus[c] ID Rate, Cases per 1000 Patient-Months
Total	961	906	1.061	0.97–1.17	.216	741
Asthma	10.5	5.0	2.078	0.73–8.70	.229	8.1
Bronchitis	28.7	33.6	0.854	0.53–1.44	.532	26.3
Chickenpox/varicella	10.8	8.4	1.293	0.54–3.81	.596	7.5
Conjunctivitis	15.1	16.8	0.901	0.47–1.91	.768	12
Contact dermatitis	14.7	13.4	1.097	0.54–2.53	.812	8.7
Cough	43	38.6	1.114	0.73–1.79	.636	41.4
Diarrhea	32.9	28.5	1.155	0.70–2.01	.588	26.4
Ear infection	30.2	23.5	1.287	0.75–2.37	.385	18.9
Gastroenteritis	14.7	16.8	0.877	0.46–1.86	.713	11.7
Hypersensitivity	12.8	6.7	1.905	0.76–6.39	.223	5.6
Impetigo	10.8	13.4	0.808	0.39–1.90	.595	7.2
Influenza	8.1	11.7	0.693	0.31–1.76	.400	7.3
Nasopharyngitis	128	114	1.121	0.87–1.47	.392	105
Otitis media	21.7	20.1	1.078	0.60–2.11	.814	20.7
Pyrexia	82.5	70.5	1.171	0.85–1.65	.350	70.1
Rhinitis	48.8	41.9	1.164	0.77–1.83	.488	27.3
Teething	71.3	35.2	2.023	1.32–3.27	.002	35.5
Tonsillitis	10.5	8.4	1.247	0.52–3.68	.650	8.2
Upper respiratory tract infection	60.1	65.4	0.918	0.65–1.32	.632	47.9
Urticaria	8.9	10.1	0.885	0.38–2.40	.790	5.1
Vomiting	19.0	18.5	1.029	0.56–2.08	.933	13.9

[a] $N = 495$; follow-up total: 2581 months.
[b] $N = 193$; follow-up total: 596 months.
[c] $N = 1098$; follow-up total: 7686 months.

site reactions, with ID rates of 2.0 and 1.2 cases per 1000 patient-months of follow-up monitoring, respectively. In study 0315/0315-E1, in which 76 infants (3–23 months of age at the time of inclusion in the DB phase) and young children were treated intermittently with 1% pimecrolimus cream for up to 2 years,[39] the most common adverse events showed a tendency to decrease in incidence over time.[39]

Effects on the Immune System

The incidence of systemic infections and skin infections was analyzed to detect any possible sign of immunosuppression associated with the use of 1% pimecrolimus cream. The analysis of adverse events described above showed no statistically significant difference in the ID rates for the most frequently reported systemic infections between the pimecrolimus DB group and the vehicle DB group (Table 3). The ID rate of total nonskin infections among patients treated with 1% pimecrolimus cream during the DB studies and DB phases was similar to that estimated for patients who received the vehicle (relative risk: 1.015; 95% CI: 0.88–1.18; $P = .842$). The ID rates for total bacterial, fungal, parasitic, and viral skin infections were also comparable in the pimecrolimus DB and vehicle DB groups (Table 4). Considering specific skin infections, the most frequently reported were impetigo and chickenpox/varicella, with no significant differences in the ID rates between patients treated with 1% pimecrolimus cream and patients who received the vehicle during the DB studies and DB phases (Tables 3 and 4).

It has been reported that patients with AD are at higher risk of herpes simplex infections, compared with the general population.[47–49] The ID rate of herpes simplex virus skin episodes, including eczema herpeticum and severe initial infections, among children with AD has been estimated to be 4.7 cases per 1000 patient-months of follow-up monitoring (95% CI: 2.6–7.7) (unpublished report on file at Novartis Pharma AG). The ID rates of herpes simplex virus infections, not including eczema herpeticum, observed during the DB phases of the studies were 0.8 cases per 1000 patient-months in the pimecrolimus group and 1.7 cases per 1000 patient-months in the vehicle group (relative risk: 0.462; 95% CI: 0.04–9.93; $P = .528$). The ID rate in the total pimecrolimus group, including DB and OL phases, was 0.9 cases per 1000 patient-months of follow-up monitoring. Eczema herpeticum is a form of herpes simplex virus infection with extensive skin involvement, occurring predominantly among patients with AD.[47,49] The

TABLE 4 **ID Rates (Cases per 1000 Patient-Months of Follow-Up Monitoring) for Skin Infections With ID Rates of ≥2 Cases per 1000 Patient-Months and Herpes Infections in Any Group, With Relative Risk, 95% CI, and *P* Values**

Skin Infections	Pimecrolimus DB[a] ID Rate, Cases per 1000 Patient-Months	Vehicle DB[b] ID Rate, Cases per 1000 Patient-Months	Relative Risk	95% CI	*P*	Total Pimecrolimus[c] ID Rate, Cases per 1000 Patient-Months
Overall	71.3	63.8	1.118	0.80–1.61	.531	46.6
Bacterial						
Total	25.6	25.2	1.016	0.60–1.85	.956	15.6
Bacterial infection	6.2	6.7	0.924	0.34–3.22	.887	3.3
Impetigo	10.8	13.4	0.808	0.39–1.90	.595	7.2
Stye	3.1	0	NE	NE	NE	1.0
Fungal						
Total	14.3	6.7	2.136	0.86–7.13	.149	8.1
Candida	3.1	0	NE	NE	NE	2.1
Oral candidiasis	5.4	3.4	1.616	0.45–10.3	.525	3.0
Skin fungal infection	3.5	3.4	1.039	0.27–6.82	.961	2.1
Parasitic						
Total	1.9	3.4	0.577	0.12–4.03	.511	0.8
Scabies infestation	1.9	3.4	0.577	0.12–4.03	.511	0.8
Viral						
Total	19.0	11.7	1.616	0.78–3.91	.235	15.0
Chickenpox/varicella	10.8	8.4	1.293	0.54–3.81	.596	7.5
Molluscum contagiosum	1.5	0	NE	NE	NE	2.2
Viral rash	4.3	1.7	2.540	0.49–46.4	.372	2.2
Herpes simplex	0.8	1.7	0.462	0.04–9.93	.528	0.9
Eczema herpeticum	1.2	0	NE	NE	NE	1.3
Nonspecified						
Total	10.5	16.8	0.623	0.31–1.35	.202	7.2
Skin infection	5.8	11.7	0.495	0.21–1.30	.124	2.9
Superinfection	2.7	3.4	0.808	0.20–5.42	.791	2.7

NE indicates not estimable.

[a] $N = 495$; follow-up total: 2581 months.

[b] $N = 193$; follow-up total: 596 months.

[c] $N = 1098$; follow-up total: 7686 months.

actual incidence of eczema herpeticum among infants with AD is unknown. In total, 10 infants treated with 1% pimecrolimus cream in the 6 clinical studies experienced clinically diagnosed eczema herpeticum. This translates into an ID rate of 1.3 cases per 1000 patient-months. For none of the patients was the diagnosis confirmed with virologic culture, polymerase chain reaction assay for viral DNA, or immunofluorescence analysis with virus-specific antibodies. Six of these cases were reported as serious adverse events. All of the patients affected were using 1% pimecrolimus cream. Five patients had severe or very severe AD at baseline, as defined with the Investigator's Global Assessment.[30] Eight cases occurred within the first 3 months of treatment with 1% pimecrolimus cream, and 6 were suspected to be treatment related. Treatment with 1% pimecrolimus cream was interrupted for 8 of 10 patients and was discontinued permanently for 1 of 10 patients. All cases resolved with topical and/or systemic antiviral therapy, without sequelae, and there was no recurrence. The ID rate for eczema herpeticum for infants in the total pimecrolimus group was 1.3 cases per 1000 patient-months of observation, which seemed to be similar to the ID rate for eczema herpeticum of 1.37 cases per 1000 patient-months of observation calculated for children >2 years of age who were treated with 1% pimecrolimus cream (unpublished data on file at Novartis Pharma AG).

Molluscum contagiosum is another viral skin infection known to affect more frequently patients with AD than the general population, with a reported incidence of 4%.[49] The ID rate for this infection among all of the infants treated with 1% pimecrolimus cream in the 6 studies (total pimecrolimus group) was 2.2 cases per 1000 patient-months of observation. No case of molluscum contagiosum was reported among patients who received the vehicle during the DB studies or DB phases (Table 4).

Other specific skin infections, which occurred less frequently than those listed in Table 4, were reported with similar ID rates among patients treated with 1% pimecrolimus cream and patients who received the vehicle during the DB studies and DB phases, with the exception of furuncle, genital bacterial infection, *Candida* diaper rash, fungal rash, tinea cruris, and skin papilloma, which occurred only among patients treated with 1% pimecrolimus cream. The ID rates of these infections in the total pimecrolimus group were ≤0.8 cases per 1000 patient-months of observation.

During the DB studies and DB phases, serious skin infections were reported for 0.8% of patients treated with 1% pimecrolimus cream and 1% of patients who received the vehicle. The ID rates of treatment-related skin infections, as assessed by investigators, were comparable in the pimecrolimus DB group and the vehicle DB group (relative risk: 0.495; 95% CI: 0.21–1.30; $P = .124$). Only 9 patients (0.8%) in the total pimecrolimus group withdrew from the studies because of skin infections. Among infants treated with 1% pimecrolimus cream for up to 2 years (study 0315/0315-E1),[39] skin infections were not more frequent during the second year of treatment than during the first year, and the incidence of all bacterial and viral skin infections was low, compared with the incidence of these infections reported in studies in which pediatric patients with AD who were receiving conventional treatment were monitored for >12 months.[47,50]

To evaluate more completely the systemic immunosuppressive potential of 1% pimecrolimus cream, its effect on the immune response to vaccinations was assessed among 91 infants and young children who completed the 1-year DB study 0315 and then were monitored for an additional 1 year (study 0315-E1).[40] At inclusion in the DB study, the majority of patients (58 of 91 patients, 63.7%) had moderate AD, and the mean percentage of TBSA affected by AD lesions at baseline was 27.6%. Seventy-six of these 91 patients had received 1% pimecrolimus cream and 15 had received control treatment (vehicle plus use of moderately potent TCSs in case of severe flares) in the first year. During the second year, all patients were treated with 1% pimecrolimus cream at the first sign or symptom of AD and as long as signs or symptoms of the disease persisted. Serum concentrations of antibodies against tetanus, diphtheria, measles, and rubella were measured at months 18 and 24. The overall proportions of patients with protective antibody titers against tetanus, diphtheria, measles, and rubella were compared with the seroprevalence reported for general, age-matched, pediatric populations.[51–54] The vaccination history indicated that the proportion of vaccinated patients was consistent with the published data on vaccination coverage in age-matched populations from low- and intermediate-susceptibility countries in Western Europe.[52–54] Analysis of the serum concentrations of specific antibodies revealed seropositivity rates of 94% for tetanus, 89% for diphtheria, 89% for measles, and 84% for rubella, which were comparable to rates reported in literature.[51–54] Pimecrolimus exposure at the time of vaccination was substantial; the proportion of vaccinated patients who had received pimecrolimus at the time of vaccination was 53% for tetanus and diphtheria (4 doses), 55% for measles, and 47% for rubella. There were no significant differences in the overall seropositivity rates between these patients and those who had not received pimecrolimus at the time of vaccinations. The results of a logistic regression analysis confirmed that there was no relationship between the antibody response to each vaccination and pimecrolimus exposure near the vaccination date (±28 days). Therefore, there was no relationship between the development of an appropriate

immune response to each vaccination and the use of 1% pimecrolimus cream during the vaccination period.

These results indicate that treatment with 1% pimecrolimus cream for up to 2 years in early childhood does not interfere with the ability to mount a normal immune response to vaccinations. The fact that the responses to vaccinations were similar among patients who had used 1% pimecrolimus cream before vaccinations and those who had not is important, because in clinical practice infants with AD are frequently treated with topical therapy before they are vaccinated. The lack of any effect of pimecrolimus on the development of an immune response to vaccination may be attributable to the low systemic exposure to this drug when it is applied topically. Therefore, the results of this study confirm the pharmacokinetic data reported above, demonstrating minimal percutaneous absorption of pimecrolimus during treatment with 1% pimecrolimus cream for up to 1 year among infants.

CONCLUSIONS

One percent pimecrolimus cream has been reported to provide treatment of AD with negligible systemic absorption.[20,27,30–32,44] The favorable safety and tolerability profile of 1% pimecrolimus cream demonstrated in published pediatric studies[35,37–39,43,44] is supported by the data summarized in this review. The combined analysis of the results from 4 pharmacokinetic studies conducted with 35 infants with AD indicated that pimecrolimus blood concentrations after topical applications were consistently low, irrespective of the level of disease severity and percentage of TBSA involved. The level of systemic exposure to pimecrolimus among infants was comparable to that observed among older pediatric patients enrolled in the same studies and treated in the same way with 1% pimecrolimus cream, which suggested that young pediatric patients are not at higher risk of significant percutaneous absorption of topically applied pimecrolimus, despite their large skin surface area/body mass ratio.

During the DB studies and DB phases, the ID rates of the majority of the most frequently reported adverse events were similar for patients who received 1% pimecrolimus cream and patients who received the vehicle. The occurrence of adverse events did not increase over time among patients treated with 1% pimecrolimus cream for up to 2 years. There was no demonstrable sign of systemic immunosuppression, because 1% pimecrolimus cream did not increase the overall incidence of systemic infections, compared with the vehicle, and its use did not affect the ability to mount a normal immune response to vaccinations.

In general, treatment with 1% pimecrolimus cream did not seem to be associated with an increased incidence of total skin infections. During the DB studies and DB phases, the ID rates of the most frequently reported skin infections and herpesvirus infections were similar for infants who received 1% pimecrolimus cream and those who received the vehicle. However, all cases of clinically diagnosed eczema herpeticum reported in the studies considered here occurred among patients receiving treatment with 1% pimecrolimus cream. In cases of suspected eczema herpeticum among patients with AD being treated with 1% pimecrolimus cream, treatment should be stopped at the site of infection and appropriate antiviral therapy should be initiated. After recovery, treatment with 1% pimecrolimus cream can be resumed. It is important to note that the risk of developing eczema herpeticum during treatment with 1% pimecrolimus cream does not seem to be particularly high among infants, because the ID rate of this infection estimated for all of the infants who received pimecrolimus in the 6 studies was similar to that observed for older children treated with 1% pimecrolimus cream.

A possible concern with the long-term use of pimecrolimus is the potential increase in the incidence rates of skin malignancies or immunosuppression-related lymphomas resulting from changes in local or systemic immunosurveillance. In preclinical studies, topical treatment with 1% pimecrolimus cream did not show any carcinogenic, photocarcinogenic, or mutagenic effects in vitro or in vivo.[41] Lymphomas related to systemic immunosuppression were observed only in animals treated with high oral doses or experimental formulations that resulted in high systemic exposure to pimecrolimus, which cannot be attained with pimecrolimus cream. The systemic exposure associated with immunosuppression (including lymphoma formation) in these animals was 31 to 343 times higher than the highest individual systemic exposure ever observed among pediatric patients with extensive AD lesions treated with pimecrolimus cream. Furthermore, no sign of systemic immunosuppression was found among infants treated intermittently with 1% pimecrolimus cream for up to 2 years; they demonstrated a normal immune response to vaccinations and did not show an increase in the incidence of systemic or skin infections over time.[39,40]

The analysis of data from clinical studies and postmarketing usage among >5 million patients treated with 1% pimecrolimus cream since December 2001 has not shown any evidence of an increased risk of cancer related to treatment with 1% pimecrolimus cream.[41] However, conclusive data will be obtained only after completion of an ongoing epidemiologic program assessing the safety of 1% pimecrolimus cream 5 and 10 years after launch.[41] Similarly, at present there are no data suggesting the possibility of an increased risk of lymphomas during treatment with 1% pimecrolimus cream. Indeed, the reported rate of non-Hodgkin lymphomas among patients treated with 1% pimecrolimus cream is well below the incidence rates for these lymphomas in the

general population.[41] Again, however, conclusive data will be obtained only after completion of the epidemiologic program mentioned above. In this context, it should be noted that no long-term study has been performed on the risk of malignancies among patients with AD treated with TCSs, despite the fact that systemic corticosteroid treatment induces immunosuppression and has been associated with increased risks of skin cancer and lymphomas[55,56] and despite the evidence that TCSs can penetrate through the skin sufficiently to cause clinically evident systemic effects.[8,15]

We think this review of data from a large number of patients provides useful information on the type of side effects infants can experience during treatment with 1% pimecrolimus cream for AD and on the risk of developing those side effects. Because of the low level of systemic absorption and the good tolerability during intermittent use in the long term, 1% pimecrolimus cream may represent an alternative to TCSs for young pediatric patients, because they represent, at the same time, the segment of the population affected most frequently by AD[1,3–5] and the segment of the affected population most susceptible to the systemic effects of prolonged TCS treatment.[8,13–15]

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