REVIEW ARTICLE

Pimecrolimus in atopic dermatitis: Consensus on safety and the need to allow use in infants

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Abstract

Atopic dermatitis (AD) is a distressing dermatological disease, which is highly prevalent during infancy, can persist into later life and requires long-term management with anti-inflammatory compounds. The introduction of the topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus, more than 10 yr ago was a major breakthrough for the topical anti-inflammatory treatment of AD. Pimecrolimus 1% is approved for second-line use in children (≥2 yr old) and adults with mild-to-moderate AD. The age restriction was emphasized in a boxed warning added by the FDA in January 2006, which also highlights the lack of long-term safety data and the theoretical risk of skin malignancy and lymphoma. Since then, pimecrolimus has been extensively investigated in short- and long-term studies including over 4000 infants (<2 yr old). These studies showed that pimecrolimus effectively treats AD in infants, with sustained improvement with long-term intermittent use. Unlike topical corticosteroids, long-term TCI use does not carry the risks of skin atrophy, impaired epidermal barrier function or enhanced percutaneous absorption, and so is suitable for AD treatment especially in sensitive skin areas. Most importantly, the studies of pimecrolimus in infants provided no evidence for systemic immunosuppression, and a

comprehensive body of evidence from clinical studies, post-marketing surveillance and epidemiological investigations does not support potential safety concerns. In conclusion, the authors consider that the labelling restrictions regarding the use of pimecrolimus in infants are no longer justified and recommend that the validity of the boxed warning for TCIs should be reconsidered.

Atopic dermatitis (AD) is a common skin disease during infancy and one which imposes a considerable burden on patients, their families and society. AD is one of the first diseases encountered during human life with 45% of cases occurring during the first 6 months. Its clinical presentation in infants typically involves the face, scalp, trunk and extensor surfaces of the extremities (1, 2). AD during infancy frequently persists into later life (3), is often associated with food allergy, and may be regarded as a presenting sign for the 'atopic march', which leads to the development of other atopic conditions such as asthma and allergic rhinitis (4, 5). AD is also associated with a considerable economic burden of up to $3.8 billion each year in the USA alone (6).

The ultimate goal for the treatment of AD in infants is cure. Optimally, treatment should be initiated as early as possible to prevent the inside–outside loss of water (which leads to xerosis, fissures, pruritus and pain) and the outside–inside penetration of foreign substances (which leads to irritation and sensitization) (7, 8). Recent evidence suggests that normal appearing non-lesional skin also contains signs of subclinical inflammation, which treatments should aim to address to induce disease remission (9). Current AD treatments do not cure the disease, but instead focus on controlling and reducing its troublesome signs and symptoms. Given that AD is a chronic disease requiring treatment for many years or even decades, such treatments need to be safe and well tolerated.

Topical standard-of-care initial treatment for AD in infants includes emollients and topical corticosteroids (TCS). TCS are used on an as-needed basis to treat disease flares and may also be considered for proactive, intermittent, long-term maintenance treatment of previously affected skin to reduce the subsequent risk of relapses (9–15). The main drawbacks to TCS are their potential local and systemic side effects, including skin atrophy, impaired epidermal barrier function, and percutaneous absorption, possibly leading to impaired growth. These risks are of particular concern with prolonged continuous TCS use (16–20). Despite TCS being effective AD treatments, concern about potential side effects has led to widespread corticosteroid phobia and poor adherence to medication (21–23). In addition, few TCS have been approved for use in children under age 2 yr and then for only 3–4 wk.

Two topical calcineurin inhibitors (TCIs), pimecrolimus 1% cream (Elidel®, Meda, Stockholm, Sweden) and tacrolimus 0.03% ointment (Protopic®, Astellas, Tokyo, Japan), which selectively inhibit the synthesis of inflammatory cytokines released from T-cells and mast cells (24), have been available for the treatment of AD in patients aged 2 yr and older since 2000–2001. The use of TCIs is currently not approved in children below 2 yr of age in the USA and Europe, although pimecrolimus is approved in patients aged 3 months and older in certain other countries such as Australia and Russia. In January 2006, the Food and Drug Administration (FDA) added a boxed warning ('black box') to the labels of these TCIs to emphasize that their long-term safety has not been established, to highlight the theoretical risk of skin malignancy and lymphoma with these treatments and to stress that their use in infants <2 yr of age is not recommended (25). This black box represents the first and only time that a warning was issued based on theoretical rather than proven safety concerns. The European Medicines Agency (EMA) also advised that TCIs should be used with caution and limited to second-line use following a safety review in March 2006.

Eight years after these warnings were issued, it is timely to re-evaluate the latest clinical efficacy and safety data on TCIs in infants to assess whether the restrictions regarding their use and the safety concerns highlighted in the boxed warnings are still justified. The primary focus of this article is on pimecrolimus rather than both TCIs, as only pimecrolimus has been extensively evaluated in studies including more than 4000 infants. To date, the efficacy and safety of tacrolimus have only been evaluated in one published open-label study of 50 infants with AD previously enrolled in a pharmacokinetic investigation (26, 27). Based on the results of a literature search and on expert opinion, the authors – a task force of expert paediatricians, dermatologists and allergists – developed consensus recommendations regarding the use of pimecrolimus in infants (defined as patients <2 yr of age) and on the safety of TCIs in general.

Clinical efficacy of pimecrolimus in infants

The favourable clinical efficacy of TCIs in AD is now well established and documented in several clinical trials. Accordingly, the treatment of AD in infants with pimecrolimus leads to a substantial reduction in disease flares (28, 29). Furthermore, studies in children and adolescents with AD have shown that long-term proactive maintenance therapy with TCIs reduces the risk of subsequent relapses (9, 30–32).

Comprehensive evidence for the clinical efficacy of pimecrolimus in infants comes from six studies that were conducted in more than 4000 patients (Table 1). Of note, the Petite study enrolled the largest population of infants with AD (i.e. 2418 patients) and followed them for the longest period of time ever studied (i.e. the first 5–6 yr of life). This open-label, parallel-group study randomized patients to treatment with pimecrolimus or TCS and had a 'real-world' design in which TCS were used according to their label and in which those treated with pimecrolimus were able to briefly use TCS if needed for an

Table 1 Overview of clinical studies of pimecrolimus in infants

Study	Age group	Interventions	Study design	Duration
Petite (33)	≥3–<12 months	Pimecrolimus ($n = 1205$) TCS ($n = 1213$)	Open-label, randomized, parallel group	5 yr
Study of the Atopic March (43)	3–18 months	Pimecrolimus ($n = 546$) Vehicle ($n = 545$)	Double-blind, randomized, parallel group Open-label extension with pimecrolimus	3 yr Up to 3 yr
Kapp et al. (2002) (28)	3–23 months	Pimecrolimus ($n = 204$) Vehicle ($n = 47$)	Double-blind, randomized, parallel group	1 yr
Papp et al. (2005) (29)	3–23 months	Pimecrolimus 2 yr ($n = 76$) Vehicle 1 yr; pimecrolimus 1 yr ($n = 15$)	One-year, open-label, non-comparative extension to Kapp et al. (28)	2 yr
Ho et al. (2003) (34)	3–23 months	Pimecrolimus ($n = 123$) Vehicle ($n = 63$)	Six-week randomized, double-blind phase followed by 20-wk open-label treatment with pimecrolimus	6 months
Kaufmann et al. (2004) (35)	3–23 months	Pimecrolimus ($n = 129$) Vehicle ($n = 66$)	Four-week randomized, double-blind phase followed by 12-wk open-label treatment with pimecrolimus and 4-wk follow-up	20 wk

TCS, topical corticosteroids.

acute flare (33). The TCS used varied according to the prescribing practices in different countries and included both low (e.g. hydrocortisone acetate) and medium potency (e.g. hydrocortisone butyrate) creams and ointments.

The clinical studies of pimecrolimus in infants have shown that this TCI leads to a rapid improvement in the signs and symptoms of AD. In the Petite study, 53% of pimecrolimus-treated infants had an overall Investigator's Global Assessment (IGA) score of 0 or 1 (indicating clear or almost clear of disease) after 3 wk of treatment (Fig. 1). Similarly, the median
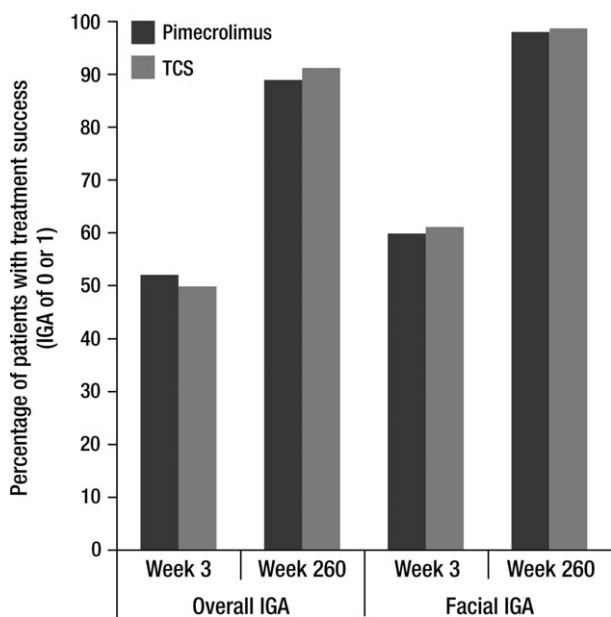

Figure 1 Percentage of patients with treatment success in the Petite study (intent-to-treat population) (33). IGA, Investigator's Global Assessment; TCS, topical corticosteroids (low and medium potency TCS were allowed according to local prescribing practices).

total body surface area (TBSA) affected by AD decreased from 16% at baseline to 4% after 3 wk of pimecrolimus treatment (33). Other studies in infants have also reported rapid and significant efficacy benefits with pimecrolimus vs. vehicle such as reductions in the mean Eczema Area and Severity Index (EASI) score and improvements in pruritus (28, 34, 35). In these studies, the majority of the clinical benefit of pimecrolimus was observed within 2 wk of treatment. Improvements in pruritus were even more rapid, occurring within 2 days (35). Rapid improvements in AD have also been observed in subgroups of infants included in real-life observational studies of pimecrolimus (36, 37).

The initial improvement in AD observed in infants treated with pimecrolimus is sustained over the long term with a progressive increase in efficacy over time. The Petite study showed that 89% of pimecrolimus-treated infants had an overall IGA score of 0 or 1 after 5 yr of as-needed treatment (Fig. 1) and that the median TBSA affected by AD decreased to 0% after 1.5 yr (33). Similar short- and long-term disease improvements were reported for patients treated with TCS in this study (51% and 92% had an IGA of 0 or 1 after 3 wk and 5 yr, respectively). Moreover, the treatment of AD in infants with pimecrolimus in the Petite study was associated with a substantial steroid-sparing effect, with pimecrolimus-treated patients using TCS for a median of 7 days compared with 178 days in the TCS group over the 5-yr study. This confirms the reduced steroid requirement observed in previous shorter-term studies of pimecrolimus (28, 29).

Of particular note, pimecrolimus is effective at treating AD affecting sensitive skin areas such as the head and neck, which are common sites of disease presentation in infants. In the Petite study, 61% of pimecrolimus- and 62% of TCS-treated infants had a facial IGA score of 0 or 1 after only 3 wk of treatment, increasing to 97% in both groups at the end of the 5-yr study (33). Similarly, other studies have shown a greater reduction in the EASI score for the head and neck region with pimecrolimus vs. vehicle (34, 35).

The effective treatment of AD in infants with pimecrolimus translates into a beneficial impact on both the quality of life (QoL) of parents and of affected infants and children (38–40). This is important as AD has a major negative impact on the QoL of the affected child and their entire family, with the impairment in QoL being greater than or equal to that caused by other common childhood diseases such as asthma (41, 42).

The Study of the Atopic March examined whether early intervention with pimecrolimus was able to affect the atopic march in a large population of 1087 infants. The study design allowed patients to initiate rescue with a mid-potency TCS if 3 days of pimecrolimus led to no improvement. The study did not show any difference between the pimecrolimus and vehicle groups in the incidence of asthma, food allergy, allergic rhinitis and allergic conjunctivitis. However, the discontinuation rate in this study was unexpectedly high following the implementation of the FDA boxed warning, and early initiation of TCS may have obscured any differences between the groups (43).

Clinical safety of pimecrolimus in infants

There is convincing evidence that TCIs have a favourable safety profile without evidence for severe adverse events (AEs) (44, 45). Application site reactions, such as burning, erythema and pruritus, were reported in <1% of infants in a pooled analysis of data from clinical studies of pimecrolimus in these patients (46). The most common AEs reported in infants treated with pimecrolimus were typical childhood infections and ailments (e.g. nasopharyngitis, pyrexia, upper respiratory tract infections and bronchitis) with a similar incidence in the pimecrolimus and control groups, and discontinuations due to AEs were typically low (<2%) (28, 29, 33–35, 43, 46). An analysis of safety data from clinical trials and post-marketing surveillance (PMS) in infants showed no increase in the risk of systemic infections with pimecrolimus (relative risk vs. vehicle [95% CI] 1.015 [0.88–1.18]) (47). Similarly, there was no increased incidence of overall skin infections with pimecrolimus in a pooled analysis of data from short-term clinical studies in infants (relative risk vs. vehicle [95% CI] 1.118 [0.80–1.61]). The risk of bacterial, fungal, parasitic or viral skin infections in these studies was also not different in the pimecrolimus- or vehicle-treated groups (Fig. 2) (46).

The primary purpose of the Petite study was to thoroughly investigate the safety of pimecrolimus in infants given that certain infections and disorders were perceived as safety signals by the FDA on the basis of statistically non-significant increases in their incidence vs. vehicle control groups in two previous pivotal studies of pimecrolimus in infants (28, 34, 48). These differences could be explained by unbalanced randomization ratios in the previous studies resulting in substantially fewer patients in the vehicle groups. In the Petite study, the crude incidence and relative risk of the infections and disorders of primary clinical interest as defined by the FDA were not different in the pimecrolimus and TCS groups (Table 2) (33). There were also no differences in the time to first occurrence of these AEs. An additional statistical analysis of AE counts for frequent events (with a repeated Poisson regression model) showed that pimecrolimus-treated patients experienced signif-
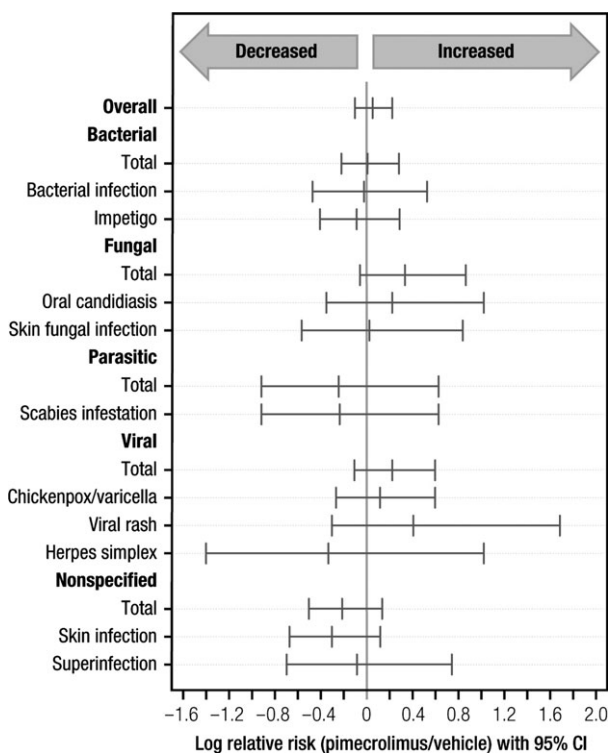

Figure 2 Relative risk for skin infections in infants based on the incidence density rates (per 1000 patient-months of follow-up) in pimecrolimus and vehicle groups (46). CI, confidence interval.

icantly more events of bronchitis (p = 0.02), infected eczema (p < 0.001), impetigo (p = 0.045) and nasopharyngitis (p = 0.04). These increases were not considered clinically significant as the differences in the incidence of these events between groups were only 2–4%, and there was no statistical adjustment for the multiplicity of comparisons (33). Consequently, it was considered that the initial safety concerns from the FDA were not supported by the Petite study data.

Pharmacokinetic studies of pimecrolimus in infants and children up to 1 yr in duration demonstrated that there is minimal systemic exposure following topical application of this calcineurin inhibitor, even in patients with extensive disease (49–53). The minimal systemic absorption of topically applied pimecrolimus is due to its high molecular weight and lipophilicity (54). In contrast, even short-term topical application of hydrocortisone cream 1% (4–106 g) in children can result in an increase of cortisol plasma levels (55), although systemic exposure with more recently developed TCS such as fluticasone propionate is lower (56). The systemic absorption of TCS is highest on thin delicate skin sites such as the face where it is 300 times greater than the plantar aspect of the foot (57).

Importantly, the clinical studies of pimecrolimus in infants have not revealed any evidence of systemic immunosuppression. Extensive immunological assessments in the Petite study showed that pimecrolimus has no effect on the developing immune system. Neither pimecrolimus nor TCS had an effect

Table 2 Crude incidence and relative risk for AEs of primary clinical interest during the 5-yr Petite study (safety population) (33)

| AE | Crude incidence (%) | | Relative risk (95% CI) |
	Pimecrolimus (n = 1205)	TCS (n = 1213)	
Influenza	6.9	5.7	1.346 (0.90–2.01)
Teething	14.9	14.9	1.179 (0.90–1.54)
Rhinitis	13.9	13.4	1.149 (0.86–1.54)
Nasopharyngitis	59.0	58.9	1.146 (1.01–1.30)
Gastroenteritis	28.2	27.1	1.146 (0.97–1.35)
Otitis media	34.7	31.7	1.135 (0.95–1.35)
Vomiting	22.5	21.3	1.116 (0.91–1.37)
Pyrexia	48.9	49.9	1.104 (0.96–1.26)
Diarrhoea	31.9	31.4	1.081 (0.92–1.27)
Cough	29.9	30.4	1.051 (0.87–1.27)
Pharyngitis	17.8	19.0	0.991 (0.75–1.31)
Hypersensitivity	2.0	1.9	0.989 (0.46–2.13)
Upper respiratory tract infection	32.0	31.2	0.937 (0.74–1.18)
Eye infection	0.3	0.3	0.871 (0.21–3.53)
Rhinorrhoea	6.8	6.8	0.804 (0.55–1.17)
Wheezing	5.6	5.3	0.752 (0.44–1.29)
Lower respiratory tract infection	3.7	4.5	0.749 (0.46–1.23)
Viral rash	3.0	4.1	0.719 (0.46–1.12)

AE, adverse event; CI, confidence interval; PIM, pimecrolimus 1% cream; TCS, topical corticosteroids.
Relative risk based on incidence density rate (pimecrolimus vs. TCS) and 95% CI was estimated from a Poisson regression model; incidence density ratio was calculated as 1000*total number of events/total monitoring time in months.

on T-cell or B-cell functions (33). Both the Petite study and a previous 2-yr study showed that the responses to childhood vaccinations (e.g. tetanus, diphtheria, measles, varicella and hepatitis B) were normal in pimecrolimus-treated infants with AD (33, 58).

A major concern of TCS, in particular when used for long-term treatment, is their potential to impair the epidermal barrier function and to cause skin atrophy. This is of special concern in infants as their epidermis is 20% thinner than that of adults (59). TCIs do not affect epidermal barrier function or cause skin atrophy as, unlike TCS, they do not affect fibroblast function and collagen production (24, 60, 61). A summary of studies which have compared prolonged use of pimecrolimus and TCS on the skin barrier is shown in Table 3. In contrast to TCS, pimecrolimus had no effect on the epidermal structure and lipid lamellae (19). Both TCS and pimecrolimus improved stratum corneum integrity and cohesion as well as epidermal differentiation as measured by expression of filaggrin (19, 20).

Black box safety concerns

A compelling body of evidence now exists which does not support the safety concerns in the boxed warnings for TCIs. These warnings state that the long-term safety of TCIs has not been established and that rare cases of skin malignancy and lymphoma have been reported in patients using TCIs (48, 62). The warnings advise against long-term use of TCIs and emphasize that they are not indicated for use in children <2 yr of age. The labels also state that an increased risk of infections, lymphomas and skin malignancies has been observed following prolonged systemic use of calcineurin inhibitors in animal studies and in transplant patients after systemic immunosuppression (48, 62). In addition, the labels for TCIs highlight that their long-term safety has not been established beyond 1 yr of non-continuous use (48, 62). Although 'long term' is not specifically defined, the results of the Petite study have shown that 5 yr of intermittent pimecrolimus use is not associated with any of the mentioned safety signals (33).

More than 8 yr after the black box warning was introduced, there is still no evidence to suggest that TCIs cause skin malignancies or lymphoma (25). The systemic absorption that was documented in pharmacokinetic studies of these agents was far too low to cause a sustained systemic immunosuppression, which is required for the development of lymphomas (27, 49–53, 63, 64). Pre-clinical investigations initially suggested that exposure to high systemic levels of TCIs – much greater than can be achieved through topical application of humans – may result in the development of animal lymphomas (25, 48, 62). One 13-wk study showed that topical application of pimecrolimus in an ethanolic solution at 47 times the maximum recommended human dose (based on area under curve

Table 3 Effect of prolonged use of pimecrolimus and TCS on skin barrier

Property	Investigations	TCS effect	Pimecrolimus effect	References
Epidermal structure/thickness	Optical coherence tomography, ultrasound and histology	−ve	Neutral/?+ve	Aschoff et al. (2011) (18) Queille-Roussel et al. (2001) (17)
Lipid bilayers and lipid lamellae	Transmission electron microscopy	−ve	Neutral/?+ve	Jensen et al. (2009) (19)
Stratum corneum integrity and cohesion	Transepidermal water loss	+ve	+ve	Jensen et al. (2009) (19)
Epidermal differentiation	Expression of filaggrin and loricin	+ve	+ve	Jensen et al. (2009) (19) Jensen et al. (2012) (20)
Antimicrobial peptide expression	Enzyme-linked immunosorbent assay	−ve	?−ve	Jensen et al. (2011) (91)

TCS, topical corticosteroids.

comparisons) resulted in lymphoma in mice (25, 48). However, the relevance of this animal model to humans is questionable as mouse skin is much more permeable to molecules of the size of pimecrolimus than human skin (65). Furthermore, in long-term carcinogenicity studies, exposure to high doses of TCIs for 2 yr did not cause any skin cancers in mice and rats (25, 48, 62). Studies in hairless mice showed that both pimecrolimus and its vehicle enhanced UV photocarcinogenesis to a similar extent compared with no topical treatment as did both tacrolimus and its vehicle, and this forms the basis for the advice in their labels to avoid or minimize sunlight exposure (48, 62). After reviewing the available data, the European Dermatology Forum stated that there is no conclusive evidence to indicate that long-term topical application of TCIs in humans is photocarcinogenic (66). Furthermore, the hairless mouse model is no longer considered useful or recommended for photosafety testing in guidance from the FDA (67). All actives and vehicles studied in this model have resulted in an increased incidence of skin papilloma in rodents.

Prolonged systemic use of calcineurin inhibitors (cyclosporine and tacrolimus) in transplant recipients can lead to lymphoma and skin cancer due to the immunosuppressive mode of action of these drugs. The risk of lymphoma is related to the intensity of immunosuppression and the resulting inability to control Epstein–Barr virus (EBV) infection (68, 69). An increasing duration and cumulative dose of immunosuppressive medication also increases the risk of skin cancer in organ transplant patients with 40% experiencing skin cancer within the first 5 yr (70, 71). Estimates suggest that the level of systemic exposure which leads to lymphoma in organ transplant

recipients is 56- to 108-fold higher than can be achieved through topical application of calcineurin inhibitors (72).

The rare cases of lymphoma identified in TCI-treated patients do not have the clinical presentation and histology that characterize lymphomas due to immunosuppression (64, 73). The typical features of immunosuppression-related lymphomas include presentation as nodal or extranodal tumours, occurrence in unusual locations, polymorphic large cell histology, the presence of EBV genome in lymphoma cells, B-cell lymphomas occurring weeks, months or years after immunomodulatory therapy, and spontaneous regression after therapy is stopped (65, 73). It is possible that the patients identified as having lymphoma following TCI therapy may actually have had early forms of cutaneous T-cell lymphoma which were misdiagnosed as AD (65). Of note, no cases of lymphoma were reported in the 2418 patients randomized into Petite, although the study was not powered to specifically address the risk of malignancies (33).

Five epidemiological studies involving more than 6.5 million AD patients have not provided any evidence for an increased lymphoma risk with pimecrolimus (Table 4) (25, 74–77). In the largest of these studies, which included over 3.5 million AD patients, no cases of lymphoma were identified in pimecrolimus-treated patients (76). There is also no epidemiological evidence to suggest that TCI use is associated with non-melanoma or melanoma skin cancer (78). A case–control study involving a questionnaire mailed to 5000 adults with AD reported a decreased risk of non-melanoma skin cancer in patients using TCIs (adjusted odds ratio [95% CI] 0.54 [0.41–0.69]; Fig. 3) (79). A retrospective observational cohort study

Table 4 Epidemiological studies of the lymphoma risk following exposure to topical pimecrolimus

Study	Patients (n)	Design	Risk of lymphoma with pimecrolimus
Arellano et al. (2007) (74)	293,253	Nested case–control study using PharMetrics database	No increased risk of lymphoma with pimecrolimus treatment: adjusted odds ratio 0.8; 95% CI 0.4–1.6
Arana et al. (2011) (25)	625,915	Nested case–control study using PharMetrics database (extension of previous)	No increased risk of lymphoma with pimecrolimus treatment: adjusted odds ratio 0.76; 95% CI 0.54–1.08 No increased risk of T-cell lymphoma with pimecrolimus treatment: adjusted odds ratio 0.85; 95% CI 0.25–2.90
Hui et al. (2009) (75)	953,064	Retrospective cohort study using Kaiser Permante California registries	No increased risk of T-cell lymphoma with pimecrolimus treatment: adjusted hazard ratio 2.32; 95% CI 0.89–6.07
Arellano et al. (2009) (76)	3,500,194	Nested case–control study using United Kingdom-based The Health Improvement Network database	No cases of lymphoma identified for pimecrolimus-treated patients
Schneeweiss et al. (2009) (77)	1,200,645	Propensity-score-matched cohort study using health insurance claims data	No increased risk of lymphoma with pimecrolimus compared with untreated patients: rate ratio 1.79; 95% CI 0.92–3.48 No increased risk of lymphoma with pimecrolimus compared with tacrolimus: rate ratio 1.16; 95% CI 0.74–1.82 No increased risk of lymphoma with pimecrolimus compared with TCS: rate ratio 1.15; 95% CI 0.49–2.72

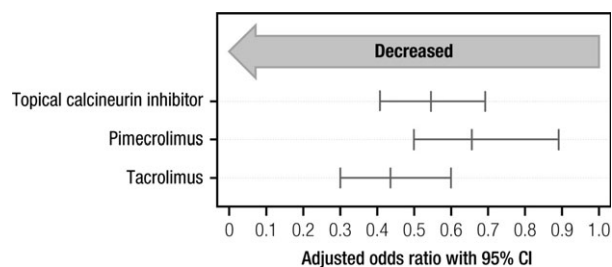CI, confidence interval; TCS, topical corticosteroids.

Figure 3 Odds ratio for non-melanoma skin cancer with topical calcineurin inhibitors (79). Odds ratio adjusted for age, gender, history of atopic dermatitis and history of non-melanoma skin cancer. CI, confidence interval.

of 953,064 AD patients did not show an association between melanoma and pimecrolimus use (adjusted hazard ratio [95% CI] 0.69 [0.37–1.28]) (75).

Post-marketing surveillance data and prospective registries have not identified an increased risk of lymphoma with TCIs (25). In the latest PMS data for pimecrolimus from 2012 to 2013, only two new cases of lymphoma have been identified (Meda data on file). In agreement with previous analyses, the small number of cases of lymphoma is below the expected background incidence in the population treated (25, 80). One previous analysis indicated that the incidence of lymphoma in pimecrolimus-treated patients identified in PMS is 54-fold less than that in the general population (0.41/100,000 vs. 22.0/100,000 patient-years of exposure, respectively) (80). Similarly, the Paediatric Eczema Elective Registry (PEER), which was initiated in 2004 to follow AD patients aged 2–17 yr treated with pimecrolimus, has only identified 4 cases of lymphoma over the past 10 yr. These cases are not the type of lymphoma that is typically related to immunosuppression.

There is currently no compelling clinical evidence to indicate that TCIs are associated with an increased risk of infections. AD patients have a pre-disposition to infections due to impairment of the skin barrier and cell-mediated immunity (81). There was no increased risk for overall skin infections in clinical studies of pimecrolimus in paediatric patients (relative risk vs. vehicle [95% CI] 0.78 [0.62–1.00]), although there may be a slightly increased risk for viral skin infections (1.80 [0.98–3.62]), in particular eczema herpeticum (47). In clinical studies of pimecrolimus in adult patients, there was no increase in the risk for overall skin infections (relative risk vs. vehicle [95% CI] 1.3 [0.9–1.8]) or viral skin infections (relative risk vs. vehicle [95% CI] 1.1 [0.7–2.0]) (44). Similarly, there is no evidence for an increase in the risk of cutaneous infections with long-term tacrolimus treatment (82).

Discussion

Currently, there is a paradox in the health care of infants with AD. The burden of disease is greatest in infants, and early disease control may prevent AD persistence into later life and possibly the atopic march to allergic rhinitis and asthma (83). However, only TCS are currently approved for use in infants. There is an unmet medical need for safe and effective

alternative therapies for AD in infants, including for application on sensitive skin areas such as the face where the disease commonly presents. Current labelling restrictions in the USA and Europe, however, prevent the use of TCIs in infants, despite the wealth of data demonstrating the clinical benefits and safety in this age group, especially of pimecrolimus.

The labelling restrictions for TCIs mean that many infants with AD who are uncontrolled with or intolerant to TCS have no treatment alternative. In addition, the long-term safety of TCS in infants has not been specifically studied and their use is restricted to 4 wk or less depending on the specific TCS and its country-specific label (25). In contrast, the long-term safety of pimecrolimus has been extensively investigated in clinical trials up to 5 yr in duration (33, 43, 46). This TCI does not cause skin atrophy and is recognized as an effective treatment for sensitive skin areas (17, 84). Currently, there are no valid safety concerns regarding the use of pimecrolimus to justify withholding it from infants.

The adverse effects of TCS encourage many parents of children with AD to use herbal creams. Many of these contain potent and super potent TCS, allergens and irritants and may be contaminated with pathogenic bacteria (85, 86). A large epidemiological study from the USA demonstrated an increased prevalence of AD in children who were treated with herbal and other alternative therapies (87). The use of pimecrolimus would be a much safer alternative to TCS than herbal topical products.

Since the introduction of the boxed warning for TCIs almost a decade ago, no compelling evidence has become available to support a causal link between their use and an increased risk of lymphoma or skin malignancy. Their safety has been comprehensively established through clinical studies, epidemiological investigations and PMS (25, 33, 43, 44, 74–77). Concerns regarding an increased risk for cancer after topical use of calcineurin inhibitors are theoretical only. Indeed, the evidence available to date indicates that the benefits of TCIs for the treatment of AD far outweigh any potential or theoretical risks. The safety of TCI therapy has also been widely recognized by many professional dermatology and paediatric organizations (15, 88–90).

The boxed warning for TCIs has had a far-reaching negative impact on paediatric patients with AD. Although only based on a theoretical risk, the decision to impose this warning has resulted in barriers to patient access and reimbursement for TCIs put in place by insurers and other payers, and a reluctance of physicians to prescribe TCIs due to factors such as an increased administrative burden and fear of litigation. This FDA warning has led to TCIs being withheld from infants with AD who have the greatest burden of disease, as well as denying other children and adults with AD access to effective therapies on the grounds of a theoretical, but unproven, safety risk. The warning has generated fear for patients (and their families) who are using or considering using TCIs. Finally, the black box has had a negative impact on clinical research programmes for TCIs in infants and paediatric drug development programmes in AD in general.

Consensus recommendations

Based on the current review of the literature and their clinical experience, the authors conclude that pimecrolimus cream and, based on more limited published reports, tacrolimus ointment, are safe and effective for the treatment of infants at least 3 months of age with AD. The authors consider the current labelling restrictions regarding TCI use in this population in Europe and the USA are no longer justified. In particular, TCIs are suitable for the treatment of sensitive skin areas in infants such as the face, which is a common site of disease presentation. Furthermore, based on the extensive evaluations into the safety of TCIs over the past 8 yr, the authors recommend that regulatory authorities should remove the current boxed warnings as this will allow AD patients to have access to effective medications with comprehensively established safety profiles.

Acknowledgments

Conflicts of interest

Thomas Luger has given lectures for Astellas; and has given lectures, been an advisory board member, and conducted studies for Meda and Novartis. Mark Boguniewicz has previously been an investigator for Novartis and Astellas-sponsored trials. Warner Carr has been a speaker for AZ; a speaker and advisor for Meda and TEVA, and an advisor for Merck. Michael Cork has been an advisory board member and given lectures for Meda, Novartis and Astellas; and has conducted studies for Novartis and Astellas. Mette Deleuran has been an advisory board member and given lectures for Meda and Astellas. Lawrence Eichenfield has been an investigator for Astellas (no honorarium) and a consultant for Valeant. Regina Fölster-Holst has given lectures and conducted studies for Astellas and Novartis. Carlo Gelmetti has been an advisor for La Roche-Posay; a speaker and an advisor for Bayer, Beiersdorf, and Pierre-Fabre; and a speaker for Meda. Adelaide Hebert has served on the DSMB for Novartis and Valeant; has given lectures for Astellas; and has received previous research funding from Astellas, Novartis, and GlaxoSmithKline with all monies paid to the University of Texas Medical School-Houston, Houston, Texas. Antonella Muraro has been a speaker and advisor for Meda; and an advisory board member for Nutricia. Arnold Oranje has been an advisor for La Roche Posay, GSK-Stiefel, Johnson & Johnson (advisory board study), Procter & Gamble and Pierre Fabres (Propranolol board); has given lectures in the last 2 years for Fagron, La Roche Posay, Meda and Texamed; and has received support for studies from Fagron bv, Molnlycke and Schering-Plough. Amy Paller has been an investigator for Astellas (no honorarium). Carle Paul was a former consultant and investigator for Novartis and Astellas. Luis Puig has been an advisory board member for Meda; and a former consultant and investigator for Novartis. Johannes Ring has been an advisory board member for Novartis, Astellas, and Meda. Elaine Siegfried has been a consultant for Valeant. Jonathan Spergel has been an advisory board member for Novartis. Alain Taieb received a grant from Astellas for an ongoing study in vitiligo. Antonio Torrelo has been an advisory board member and given lectures for Meda; and has given lectures for Astellas. Thomas Werfel has given lectures for Meda and Astellas. Ulrich Wahn has received a consultant fee from Bayer Consumer Care. Philippe Eigenmann, Harald Gollnick, Eckard Hamelmann and Georg Stingl report that they have no conflicts of interest to declare.

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