

Unmet medical needs in the treatment of atopic dermatitis in infants: An Expert consensus on safety and efficacy of pimecrolimus

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Abstract

Atopic dermatitis (AD) is a common skin disease during infancy, which imposes a considerable burden on patients, their families, and the society, requiring effective treatment options that result in rapid and sustained symptom relief. Additionally, early treatment may prevent the development of atopic comorbidities by restoring the skin barrier. Currently, topical standard-of-care for AD in infants includes emollients and topical corticosteroids (TCS) to treat and reduce the risk of flares. However, only few have been approved for infants and long-term maintenance therapy with TCS is not indicated due to potential local and systemic side effects, including skin atrophy. Accordingly, the recently updated European guidelines for treatment of AD recommend topical calcineurin inhibitors (TCIs) for long-term use, treatment of sensitive skin areas, and for use in the pediatric population. Evidence on the use of TCIs for infants has almost been exclusively collected for pimecrolimus, with >4,000 infants evaluated in clinical trials, consistently confirming that pimecrolimus is a safe and effective treatment for infants with AD. Nevertheless, its use is still restricted in most countries to children above the age of 2 years due to initial and mostly theoretical safety concerns. Based on a careful review of the available evidence of clinical trials, post-marketing surveillance, and epidemiological studies, an Expert Panel of European dermatologists and pediatric allergologists concluded that these safety concerns are no longer valid. Therefore, pimecrolimus offers a safe and effective alternative to TCS in infants aged 3 months and above, and labeling restrictions in this age group are no longer justified.

Keywords

Atopic dermatitis, pimecrolimus, infant, safety, efficacy

Key Messages

This narrative review compiles evidence that has been generated during the last 20 years on the use of pimecrolimus 1% cream in infants for the treatment of atopic dermatitis. The authors believe this work is of interest to the readers of Pediatric Immunology & Allergy, since use of pimecrolimus is still restricted to children aged 2 years and above in most countries, including European countries. According to the evidence and the opinion of the authors there is currently no reason to support this restriction any longer. The authors hope this review will convince the readers to initiate treatment of atopic dermatitis already during infancy and to consider topical pimecrolimus as an alternative to topical corticosteroids for the treatment of atopic dermatitis in infants aged 3 months and above.

Abbreviations

AD: atopic dermatitis; AEs: adverse events; CI: confidence interval; EASI: Eczema Area and Severity Index; EMA: European Medicines Agency; FDA: Food & Drug Administration; HR: hazard ratio; IGA: Investigator's Global Assessment; LoQ: limit of quantification; MAS: Multicenter Allergy Study; NMSC: nonmelanoma skin cancer; OR: odds ratio; PEER: Pediatric Eczema Elective Registry; QoL: quality of life; RCT: randomized controlled trial; RR: relative risk; SAM: Study of the Atopic March; TBSA: total body surface area; TCIs: topical calcineurin inhibitors; TCS: topical corticosteroids

Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory dermatoses, occurring often in families with atopic predisposition and other atopic diseases (1). Pruritus and eczematous lesions are important clinical manifestations of AD, with pruritus being the most debilitating symptom of the disease (2-4). The distribution and morphology of the lesions vary with age, and especially during infancy sensitive skin areas, such as the face, neck, and scalp, are affected (1, 5). Although the pathophysiology of AD is not completely understood, accumulating evidence suggests a complex interplay between genetic, immunological, and environmental factors contributing to impaired epidermal barrier function and allergic inflammation (1, 5-8). The worldwide prevalence of AD ranges between 10 and 20% in the pediatric population, depending on the geographic region (9, 10). Among patients with AD, the majority have an onset in infancy, with about 73% presenting symptoms before the age of 2 years, underscoring the importance of early effective and safe management in the infant age group (7, 11, 12). Furthermore, persistence of AD is prolonged with age of onset, as patients who were diagnosed between the ages of 0 to 1 year or between the ages of 6 to 11 years had a median persistence of AD of 3 or 12.5 years, respectively (13). Currently, AD cannot be cured and management focuses on restoring the disturbed epidermal barrier function and tempering the inflammatory skin responses, to ultimately treat and reduce the risk of flares on the long-term (14). The recently published consensus-based European guidelines for treatment of AD, recommend topical corticosteroids (TCS) as first-line anti-inflammatory therapy in infants with mild-to-moderate AD (14). However, TCS are associated with several limitations due to potential local side effects, including skin infections, impairment of the epidermal barrier function, and skin atrophy, which limit their use for treatment of sensitive skin areas (14, 15). Additionally, percutaneous absorption of TCS through the disrupted skin may lead to systemic exposure and subsequent growth impairment (15). As a result of these safety limitations, adherence to TCS is often poor due to corticophobia (14, 16). The topical calcineurin inhibitors (TCIs) – pimecrolimus 1% cream (Elidel[®], Meda, Stockholm, Sweden) and tacrolimus 0.03% and 0.1% ointment (Protopic[®], Astellas, Tokyo, Japan) – are another class of anti-inflammatory drugs, which are indicated for mild-to-moderate and moderate-to-severe AD, respectively (17-20). TCIs have a more selective mechanism of action compared to TCS and do not cause impairment of the epidermal barrier function and skin atrophy (14, 21, 22). Therefore, the European guidelines for treatment of AD recommend TCIs for use in sensitive skin areas as well

as for long-term treatment (14). Evidence from clinical trials on the use of TCIs for the treatment of AD in infants mostly exists for pimecrolimus. Based on this evidence, pimecrolimus is approved in infants aged [?]3 months in 10 countries (Elidel^(r) [pimecrolimus] cream 1%, Prescribing Information [Australia, Brazil, Canada, India, Indonesia, Israel, New Zealand, Philippines, Russia, and Thailand]). However, pimecrolimus is currently not approved in Europe and the United States (US) in children below the age of 2 years due to initial safety concerns. In 2006, the Food & Drug Administration (FDA) added a black-box warning to the TCIs labels to emphasize that long-term use has not been established, warning about a theoretical increased risk of lymphoma and skin malignancies, and indicating that use of TCIs in infants is not approved (17). In the same year, the European Medicines Agency (EMA) limited the use of TCIs to second-line treatment of AD following a safety review (18). During the last 20 years, both the short- and long-term safety of pimecrolimus for the treatment of AD in infants has been extensively evaluated. Furthermore, a previous recommendation from an international group of dermatologists already concluded in 2015 that use of pimecrolimus should no longer be restricted to children above the age of 2 years (23). This review aims to provide the rationale behind the high need to initiate treatment of AD during infancy and to update the previous consensus guidance on the use of pimecrolimus in infants between 3 months and 2 years of age.

Methods

Here, we present the findings from a virtual meeting held in May 2020 attended by nine European Experts in AD. An updated consensus guidance was developed based on a review of the latest available evidence on the use of topical pimecrolimus 1% cream in infants aged between 3 months to 2 years from clinical trials, including the results from 5-year PETITE study which assessed the long-term safety and efficacy of pimecrolimus versus TCS in over 2,000 infants. Additionally, post-marketing surveillance and epidemiological studies were critically evaluated. Ultimately, the comprehensive appraisal of the evidence was combined with the opinion of the Expert Panel on the prevailing medical need for safe and effective treatment options in infants with AD to decrease the significant disease burden and improve the quality of life (QoL) of patients and their families.

Rationale for early treatment initiation of AD during infancy

AD is not a stand-alone disorder, but is associated with a variety of comorbidities, including progression of atopic manifestations, known as the atopic march. Although results on the existence of a sequential atopic march have been inconsistent, a growing body of evidence supports that children with AD are at high risk of developing various atopic comorbidities including food allergy, asthma, and allergic rhinitis (24-31). The most apparent association is found between AD and sensitization to food allergens (24, 27, 28, 31). The mechanism behind the increased susceptibility to food allergy in patients with AD remains to be deciphered and is multifactorial, such as the pathogenesis of AD itself (28, 31, 32). Regardless of the mechanism, earlier onset and more severe disease are important risk factors for the development of usually multiple food allergies, arguing for preventative treatment strategies of AD during infancy (27, 33, 34). To address this hypothesis, a recent multicenter, randomized controlled trial (RCT), including 1,394 newborns, assessed the impact of daily emollient use during the first year of life to prevent AD as well as food allergy and other atopic comorbidities (35). Unlike other reports, emollients were not able to prevent AD, indicating that more effective treatment options may be needed to restore the skin barrier in infants who are at high risk to develop AD and subsequent atopic comorbidities (35).

The classical course of the atopic march, which progresses from AD to food allergy, allergic rhinitis, and ultimately asthma, has been challenged over the years. However, there is an undoubtable association between these atopic comorbidities, as already has been discussed for AD and food allergy. Although not every child with AD will be sensitized to inhalant allergens, several birth cohort studies have demonstrated that onset of AD during infancy, AD severity, and parental atopy are strong predictors to develop allergic rhinitis and

asthma later in life (12, 25, 26, 36). The German Multicenter Allergy Study (MAS) is until now the longest birth cohort study, which followed up patients until the age of 20 years (26, 36). The MAS demonstrated that AD, asthma, and allergic rhinitis particularly coexist as a multimorbidity in patients who have parents with allergies, implying the importance of yet to be fully determined genetic factors (26, 37). More longitudinal studies are still warranted to understand if treatment at first signs and symptoms during infancy may prevent the allergic multimorbidity, especially in those who are at risk to develop atopy.

Additionally, AD was found to be associated with comorbidities beyond the atopic march, including cardiovascular and neuropsychiatric disorders (38-40). The latter comorbidity is mostly driven by the impact of AD on the whole family, particularly so on the QoL of young children and their caregivers (2, 38, 41). Itching and scratching are the most distressing early symptoms of the disease, which can lead to sleeplessness, psychological disorders, social isolation, and overall poor QoL of patients and their families (3, 42). Similar to atopic comorbidities, QoL decreases when the severity of AD increases, emphasizing the need for treatments that rapidly and sustainably relief pruritus (2).

There is also a considerable economic impact of AD on patients, patients' families, and payers. Direct costs of AD are mostly related to prescriptions, physician visits, hospital costs, and pharmacy costs (2). These direct costs were calculated to be as high as \euro927 per patient per year by a recent cross-sectional study performed in nine European countries, and pose a significant economic burden to the patient that is more pronounced compared with other chronic diseases, such as psoriasis and rheumatoid arthritis (43). Furthermore, AD is associated with a variety of indirect costs due to decreased productivity and work absenteeism, which are related to the social and psychological burden of the disease (2, 44). Paradoxically, the prevalence of AD was reported to correlate with the socioeconomic status, whereas patients with severe AD were found to have less educational attainment resulting in a lower annual income (44, 45). Consequently, improved care for AD would allow substantial savings on the short- and long-term for both patients and the society. Therefore, early treatment of AD is not only essential in treating the skin disease itself to prevent worsening, but also to prevent the development of atopic comorbidities and most importantly decrease the significant burden of AD on the entire family and the society as early as possible.

Efficacy of pimecrolimus in infants

The efficacy of pimecrolimus for the treatment of AD in infants has been extensively evaluated in multiple vehicle-controlled pivotal trials (**Table 1**). These trials have consistently demonstrated that topical pimecrolimus treatment results in effective long-term control of AD in infants (46-50). Twice-daily application of pimecrolimus in infants effectively reduced the risk for flares compared with vehicle, with 67.6% versus 30.4% of patients completing 6 months without flares ($P < .001$), resulting in an absolute risk reduction of 37.2%, which was independent of baseline severity (47). Additionally, the mean Eczema Area and Severity Index (EASI) was already reduced by approximately 70 – 80% after 4 weeks of pimecrolimus treatment, while there was no symptom relief at this timepoint for infants who were treated with vehicle control (46, 50). Furthermore, this response was irrespective of disease severity and significant even for infants with very severe disease (Investigator's Global Assessment [IGA] [?]⁴) (46). The earliest significant reduction in EASI was reported from day 4 onwards, with a reduction of 38.5% and 17.6% after 4 days of pimecrolimus and vehicle treatment, respectively ($P < .001$) (46). Importantly, the early and sustained treatment success (IGA 0 or 1) observed in the head and neck area was similar to that of the whole body. A rapid response in sensitive skin areas is especially important in infants who mostly have a sensitive skin structure to decrease the disease burden as early as possible (46). Furthermore, disease control with pimecrolimus was proven to be long-term, with approximately 70% of patients having minimal or no disease, as assessed by the IGA score and EASI, after 2 years of intermittent pimecrolimus treatment (48). Similar to the reductions seen in EASI and IGA scores, pimecrolimus effectively relieved pruritus, which was associated with significant improvements in the QoL and sleep behavior of the infant. Already within the first week of use, 70% of infant patients reported absence of mild pruritus compared to about half of the patients treated with vehicle

(46-48, 50-52). Also, parents experienced significant improvements in psychosomatic well-being, social life, confidence in medical treatment, and emotional coping after 4 weeks of treatment of their infants (51). These improvements in QoL of parents were found to be sustained up to 1 year of treatment and probably thereafter, as they coincided with long-term disease control of their infants (52). Although not evaluated in this study, such impact on QoL presumably also decreases the substantial economic burden of the disease. In the vehicle-controlled trials, use of pimecrolimus was found to decrease over the course of long-term treatment upon clearance of symptoms, but importantly discontinuation was not associated with rebound flares, as has been described for TCS (46, 48, 53). Pimecrolimus treatment also had a steroid-sparing effect in the infant, which was reflected by a decrease in overall use and an increased time to first use of TCS as well as a reduced number of days on TCS therapy (47, 49).

Head-to-head comparisons between pimecrolimus and tacrolimus in the pediatric population were assessed in two RCTs, which evaluated both treatments in children of 2 to 17 years of age (54, 55). These two trials were also included in a meta-analysis, demonstrating that pimecrolimus and tacrolimus have comparable efficacy in children with AD (56). However, to the best of our knowledge, there is only one 24-month open-label phase II clinical trial evaluating safety and efficacy of tacrolimus in 50 infants below the age of 2 years, indicating additional studies are needed to evaluate tacrolimus for the infant indication (57).

To support the use of pimecrolimus as an alternative treatment to TCS in infants, the PETITE study was designed to compare the long-term safety and efficacy of TCS and pimecrolimus for the treatment of infants with AD in a real-world setting (58). In total, 2,418 infants aged between 3 and 12 months were randomized to receive either pimecrolimus (n=1,205) or mild-to-moderate potency TCS (n=1,213) (58). However, short-term use of TCS was allowed in case disease flares could not be controlled by pimecrolimus treatment. The PETITE study confirmed the previous results from the vehicle-controlled trials, showing that pimecrolimus relieved symptoms in more than 50% of patients already after 3 weeks of treatment. The onset of disease control was comparable between pimecrolimus and TCS, and treatment with both anti-inflammatory drugs resulted in almost complete clearance of symptoms in more than 85% of patients after 1.5 years of intermittent treatment. Accordingly, less than 5% of body surface area was affected in week 3, with no eczematous lesions after 1.5 year of treatment in both groups which was maintained until the end of the study (58). Importantly, pimecrolimus was steroid-sparing, as 36% of patients in the pimecrolimus group did not use any TCS during the 5 years follow-up period (58). Whether or not the reduced need for TCS improves treatment adherence by overcoming concerns related to corticophobia remains to be formally demonstrated. However, it is well-established that use of TCS is causing epidermal thinning and skin atrophy, while pimecrolimus can restore certain aspects of the epidermal barrier (22). As infants overall have a sensitive structure of the skin, this is an additional factor favoring long-term use of pimecrolimus over TCS for infants with AD.

So far, the Study of the Atopic March (SAM) is the only RCT that examined the impact of pimecrolimus versus vehicle treatment on the development of atopic comorbidities in infants with AD (30, 33). This initial study found no effect of early pimecrolimus treatment on the development of atopic comorbidities which may be at least partially attributed to the unexpectedly high discontinuation rate (48%) due the fact that the trial was conducted just after implementation of the black-box warning for pimecrolimus (30, 33). Nevertheless, rates of food allergies, asthma, and allergic rhinitis were all lower than previously reported, not excluding an effect of early treatment (30). Additionally, most infants were not presenting with severe disease and rescue therapy with TCS was permitted in both treatment groups, which may have compromised the results (30). Due to the aforementioned limitations, it remains currently unclear whether early intervention with pimecrolimus for treatment of AD in infants may prevent the development of atopic comorbidities.

Pharmacokinetics of pimecrolimus in infants

Initial safety concerns were related to the potential systemic absorption of pimecrolimus. However, evidence from experiments in minipigs showed that the systemic bioavailability of pimecrolimus was transient and negligible, making the risk for systemic side effects not relevant (59). Furthermore, the penetration and

permeation profile of pimecrolimus was superior compared to other treatments for AD. Whereas drug concentrations of pimecrolimus in human skin were of the same order of magnitude as tacrolimus and TCS, permeation was 9-10 and 70-110 fold lower than tacrolimus and TCS, respectively, predicting lower systemic exposure (60). The pharmacokinetic (PK) profile of pimecrolimus was evaluated in six studies, which enrolled a total of 41 infants treated with pimecrolimus for 3 weeks (**Table 2**). Pimecrolimus blood concentrations were below the limit of quantification (LoQ) in the majority of samples, which was either 0.1 or 0.5 ng/mL, depending on the assay used (61-65). In the remaining blood samples, the blood concentration of pimecrolimus was below 2 ng/mL, with some exceptional outliers that were just above this limit. One study evaluated blood samples of infants aged between 5.7-11.9 months over a 1-year period of intermittent pimecrolimus treatment (63). Importantly, this study found no accumulation of pimecrolimus in infants with moderate-to-severe AD, consistently showing minimal systemic exposure even on the long-term. The impact of the total body surface area (TBSA) affected was also found to be minimal, and the difference between patients with 90% and 10% of TBSA affected was not greater than 0.74 ng/mL (62). These findings were also supported by another study, which enrolled infants with a maximum TBSA affected of 92%, but systemic pimecrolimus concentrations remained below 2.26 ng/mL in all infants after 3 weeks of treatment (65). These concentrations are far below the maximum blood concentration (54.5 ng/mL) observed in adult patients with psoriasis treated orally with 30 mg twice daily of pimecrolimus for 4 weeks, a dose that was also well-tolerated in these patients (62). An analysis of pimecrolimus blood concentrations in infants compared to older children (>24 months of age) demonstrated that infants were not a higher risk for systemic exposure of pimecrolimus, and that blood concentrations of pimecrolimus remained below the LoQ (i.e. <0.5 ng/mL) in the majority of patients, irrespective of age (66). Overall, the favorable penetration and permeation profile of pimecrolimus seen in minipigs together with the minimal systemic exposure found in the PK studies support that use of pimecrolimus in infants is safe, regardless of the TBSA affected and duration of treatment.

Safety of pimecrolimus in infants

The favorable safety profile of pimecrolimus in infants has been demonstrated in the above described vehicle-controlled trials (**Table 1**) (30, 46-48, 50, 51). Four of these trials were also evaluated in a previously pooled safety analysis (66). In this safety analysis, a total of 495 pimecrolimus-treated infants were compared with a total of 193 infants who were treated with vehicle (66). Although results of this analysis may have been confounded by larger patient numbers in the pimecrolimus treatment group, rates of adverse events (AEs) were similar between pimecrolimus and vehicle, except for teething which was more commonly observed in pimecrolimus-treated infants (66). All other AEs were disorders typically encountered during childhood, such as nasopharyngitis, pyrexia, upper respiratory tract infections, and bronchitis (66). Burning and erythema were the most frequently reported application site reactions, occurring in less than 1% of infants treated with pimecrolimus (66). Consistent with the low systemic exposure of pimecrolimus in infants (**Table 2**), the pooled safety analysis confirmed that use of pimecrolimus is not associated with immunosuppression (66). Accordingly, the incidence of non-skin infections was comparable between pimecrolimus and vehicle treatment groups (relative risk: 1.015; 95% confidence interval [CI] 0.88-1.18). The incidence rates of bacterial, fungal, parasitic, and viral skin infections were also not altered by pimecrolimus treatment (66). To further evaluate the impact of topical pimecrolimus on the developing immune system, seropositivity rates upon vaccination were assessed in 91 infants, who had applied pimecrolimus for a median number of 377.5 days during 2 years of follow-up (67). Results demonstrated that topical application of pimecrolimus in infants did not interfere with tetanus, diphtheria, measles, and rubella vaccination response (67).

Despite numerous studies demonstrating that pimecrolimus was well-tolerated in infants without evidence of immunosuppression, initial safety and tolerability concerns remained due to the lack of long-term safety data. Additional safety data were requested mainly to determine the impact of pimecrolimus on the developing immune system, and to counteract the link between pimecrolimus use and (skin) malignancies. Since the implementation of the black-box warning, the 5-year PETITE study, several epidemiological studies, post-

marketing surveillance, and the ongoing Pediatric Eczema Elective Registry (PEER), all aimed to resolve these safety concerns (58, 68-73). The PETITE study reassured that long-term use of topical pimecrolimus in infants was not related to an increased incidence of 18 AEs, which were of primary clinical interest because of safety signals reported in previous trials (58). Over the 5-year study period, there were no differences in growth rates between both treatments and not more than 1% of patients discontinued their treatment. Similarly to the results from the vehicle-controlled trials, use of pimecrolimus did not affect vaccination response of the infants. Tetanus, hepatitis B, measles, varicella, and Hemophilus influenzae type B antibody titers post vaccination were all considered normal and comparable between infants who had used pimecrolimus or TCS for the past 5 years. The PETITE study provided additional evidence that use of pimecrolimus has no impact on the developing immune system by demonstrating similar humoral and cellular immune responses with pimecrolimus and TCS (58). Furthermore, *ex vivo* studies showed that levels of CD3+ T-cells over time were comparable not only between pimecrolimus and TCS, but also with historical controls. No malignancies were observed in the pimecrolimus treatment group, and there were no cases of cutaneous T-cell lymphoma or any other skin malignancy in any of the almost 2,500 enrolled infants, out of which more than 1,000 had used pimecrolimus on the long-term (58).

Additionally, five epidemiological studies were conducted to evaluate the potential malignancy risk that is associated with the use of TCIs in general, including pimecrolimus (**Table 3**) (68-70, 72, 74). However, when interpreting results from these studies one should consider that patients with AD are generally more prone to develop cancer compared to patients without AD. This was demonstrated by a study performed in the United Kingdom (UK), comparing more than 60,000 patients with AD across all ages with more than 4 million individuals without AD. After adjusting for age and sex, patients with AD had an increased risk to develop cancer in general (75). Specifically, AD was found to be associated with increased incidences of lymphoma, melanoma, and nonmelanoma skin cancer (NMSC) (75). Even when keeping this in mind, none of the five epidemiological studies, involving more than 6.5 million patients with AD, showed an increased risk of lymphoma, including T-cell cutaneous lymphoma, in patients with AD who had been treated with pimecrolimus (**Table 3**). Consistent with these results, a meta-analysis published by Legendre et al. (2015) failed to find a correlation between pimecrolimus and risk of lymphoma when used for the treatment of AD (**Figure 1**) (76). The same was true for tacrolimus and low-potency TCS, whereas high-potency TCS were associated with a small but significant increase in lymphoma risk (**Figure 1**) (76). However, there was a high level of heterogeneity between the included studies and the results for high-potency TCS may have been biased by disease severity, as high-potency TCS are mainly used for the treatment of severe cases, which in itself is a risk factor for lymphoma (68). Similarly, there was no association between topical use of pimecrolimus and the incidence of NMSC based on a questionnaire that was sent out to 5,000 adult patients with AD out of which 1,000 had NMSC (77). Interestingly, the latter case-control study reported less cases of NMSC in patients treated with TCIs, especially with pimecrolimus (77). Because epidemiological data are retrospectively collected and studies generally had a limited follow-up time, the PEER was initiated in 2004 to prospectively gather post-marketing data in children with AD between the ages of 2-17 years (71). To be included in the registry, children had to be treated for at least 6 weeks with pimecrolimus prior to enrolment into the registry. The primary aim of this nationwide, observational registry in the US and Canada was to evaluate the possible link between topical use of pimecrolimus and malignancy over a follow-up period of 10 years (71). At the time of the first interim results, 7,457 children with AD were enrolled in the PEER for more than 25,000 person-year of follow-up. Over the 10-year study period, five malignancies had been reported (2 leukemia, 1 osteosarcoma, and 2 lymphomas) (71). These malignancies were not considered drug-related and the standardized incidence ratio for all malignancies as compared with the Surveillance, Epidemiology and End Results (SEER) data was 1.2 (95% CI 0.5-2.8), indicating that children exposed to pimecrolimus for the treatment of AD are not at risk to develop cancer (71). As of March 2020, only five additional cases of malignancies were reported in the PEER, evaluating data derived from 8,015 patients and including 45,960 person-year of follow-up (Meda data on file). Importantly, neither the interim results nor the latest follow-up data, reported any cases of skin cancer. Taken together, there is currently no clinical reason to expect malignancies when using topical pimecrolimus for the treatment of AD.

Discussion

The prevalence of AD is the highest in the infant age group and the incidence in infants continued to increase during recent years (12, 78). Because of this high prevalence and the substantial impact that the disease has on the QoL of both patients and caregivers, safe and effective treatment options for infants with AD are needed (2, 4, 42). Treatment should focus on lifelong management, providing rapid symptom relief to reduce the significant socioeconomic burden as early as possible (44). Additionally, restoration of the skin barrier by early treatment may prevent AD worsening into more severe conditions, its persistence into later life, and the progression of the atopic march (13, 24, 38, 79). Despite the well-known rationale to initiate treatment of AD during infancy, there is still an unmet medical need of alternative treatment options to TCS, which remain the mainstay of treatment in infants with AD (14). TCIs are one of these alternative treatment options, overcoming most limitations of TCS, including poor adherence due to corticophobia and rebound flares upon discontinuation (16, 46, 53). Additionally, TCIs are steroid-sparing reducing the risk of chronic exposure to TCS which may result in skin atrophy and subsequently increased percutaneous absorption of steroids in the infant, especially when used in sensitive skin areas (14, 22, 47, 49, 58). All studies, except for one, evaluating safety and efficacy of TCIs for the infant indication have been conducted with pimecrolimus. Based on the available evidence, the efficacy of pimecrolimus for the treatment of infants with AD has never been questioned and was also found to be comparable to the use of TCS in the 5-year PETITE study (58). Nevertheless, pimecrolimus is in most countries only approved as second-line treatment for short-term use in children with AD above the age of 2 years due to initial concerns about long-term safety. Safety concerns were the result from preclinical carcinogenicity studies demonstrating that systemic exposure of animals to immunosuppressant doses of TCIs resulted in malignancies (17, 80). The preclinical safety concerns were reinforced by cases of lymphoma and skin cancer in patients who were treated systemically with calcineurin inhibitors (cyclosporine and tacrolimus) after whole organ transplantation. These findings ultimately led to the inclusion of a black-box warning in the US and the second-line use of TCIs in Europe which was based on a theoretical rather than a proven risk of malignancy (17, 80). However, systemic exposure to pimecrolimus upon topical application is negligible, even in infants who have the greatest body surface area-to-weight ratio (61-63, 65). Accordingly, epidemiological studies failed to find a causal relationship between use of pimecrolimus and malignancies in patients with AD (68-70, 72, 74). However, patients included these studies often only had short or unknown exposure times to pimecrolimus without focusing on the pediatric population. Therefore, the 5-year PETITE study was designed to assess the risk on immunosuppression in infants using pimecrolimus for a median of 224.5 days (58). Based on the results from the PETITE study, topical pimecrolimus had no effect on the developing immune system and no malignancies were reported in infants treated with pimecrolimus (58). To refute the argument that the follow-up time of the PETITE study was insufficient to examine the association between pimecrolimus and malignancies, the PEER was initiated in 2004, albeit not in infants but in pediatric patients above the age of 2 years (71). The most recent results from the PEER did not report any cases of malignancies that could be related to immunosuppression and provided the ultimate evidence that use of topical pimecrolimus is not associated with an increased cancer risk ((71) and Meda data on file). Another registry similarly evaluated the long-term safety of tacrolimus ointment in children with AD. This registry confirmed that there is currently no evidence supportive of an increased long-term cancer risk in children with AD who had been treated with TCIs (81). Due to the extensive amount of studies that have been conducted to evaluate the safety of pimecrolimus for the treatment of AD in the pediatric population, data on the long-term use of pimecrolimus are now surpassing these collected for mid- to high-potency TCS (82). After nearly 20 years of clinical experience, the Expert Panel concluded accordingly that it is no longer appropriate to restrict the use of pimecrolimus to children above the age of 2 years. This is reflected particularly by the recent approval of pimecrolimus for treatment of infants with AD and the removal of the black-box warning in Canada in 2019 (83). Additionally, the recently published consensus-based European guidelines recommend long-term use of TCIs for sensitive skin areas in the pediatric population (14). Based on the available evidence and expert opinion, the European Expert Panel concludes that treatment of AD should be initiated as early as infancy, and topical pimecrolimus is a safe and effective steroid-sparing treatment option for both short and long-term use, that should no longer

be withheld from infants aged 3 months and above.

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Tables

Table 1. Overview of clinical studies evaluating topical use of pimecrolimus in infants. Studies reporting on the same patients were grouped.

Study	Age group
Kaufman et al. (2004) (46) and Staab et al. (2005) (51)	3-23 months
Kapp et al. (2002) (47), Papp et al. (2004) (49), Papp et al. (2005) (67) and McKenna et al. (2006) (52)	3-23 months
Ho et al. (2003) (50)	3-23 months
Sigurgeirsson et al. (2015) (58)	[?]3-<12 months
Schneider et al. (2016) (30) and Spergel et al. (2015) (33)	3-18 months

EASI: Eczema Area and Severity Index; IGA: Investigator’s Global Assessment; QoL: quality of life; RCT: randomized controlled trial; SCORAD: scoring atopic dermatitis; TBSA: total body surface area; TCS: topical corticosteroids; wks: weeks; yrs: years

Table 2. Overview of pharmacokinetic studies evaluating pimecrolimus in the pediatric population

Study	Duration	Number of patients	Age group
Harper et al. (2001) (61)	3 wks	10*	14-53 months
Allen et al. (2003) (62)	3 wks	8**	8-30 months (
Allen et al. (2003) (62)	3 wks	8	4-11 months (
Lakhanpaul et al. (2002) (63)	49 wks (1-yr extension to Allen et al. (2003) (62)	5	5.7-11.9 months
Staab et al. (2005) (65)	3 wks	22	3.4-22.7 months
Eichenfield et al. (2007) (64)	3 wks	17	3.6-139.2 months

* Two patients below the age of 24 months

** Three patients below the age of 24 months with TBSA >20%

*** Six patients aged between 3-23 months

§ Two samples from the same patient higher than 1 ng/mL (2.48 and 4.14 ng/mL) probably due to contamination of blood samples

Table 3. Overview of epidemiological studies evaluating cancer risk associated with different treatments in patients with AD.

Study	Number of patients	Study design	Results	Conclusion
Arellano et al. (2007) (68)	293,253	Nested case-control study (US PharMetrics database)	Adjusted OR for lymphoma: pimecrolimus vs non-use: 0.82 (95% CI 0.42-1.61) tacrolimus vs non-use: 0.79 (95% CI 0.37-1.71) low-potency TCS vs non-use: 1.06 (95% CI 0.72-1.57) high-potency TCS vs non-use: 1.23 (95% CI 0.83-1.84)	No increased risk of lymphoma in patients treated with TCS or TCIs, including pimecrolimus
Arana et al. (2011) (72)	625,915	Nested case-control study (US PharMetrics database)	Adjusted OR for lymphoma: pimecrolimus vs non-use: 0.76 (95% CI 0.54-1.08) tacrolimus vs non-use: 1.24 (95% CI 0.80-1.91) TCS vs non-use: 0.90 (95% CI 0.75-1.07)	No increased risk of overall lymphoma in patients with AD treated with TCS or TCIs, including pimecrolimus. No difference in patients below the age of 20 years
Schneeweiss et al. (2009) (69)	1,200,645	Nested case-control study (US Ingenix database)	RR for lymphoma: pimecrolimus vs non-use: 1.79 (95% CI 0.92-3.48) pimecrolimus vs tacrolimus: 1.16 (95% CI 0.74-1.82) pimecrolimus vs TCS: 1.15 (95% CI 0.49-2.72)	No increased risk of lymphoma with pimecrolimus compared to untreated patients or compared to patients treated with tacrolimus or TCS
Arellano et al. (2009) (70)	3,500,194	A nested case-control study (UK THIN database)	OR for lymphoma: patients with AD vs patients without AD: 1.83 (95% CI, 1.41-2.36) TCS vs non-use: 1.46 (95% CI 1.33-1.61) high-potency TCS vs non-use: 1.80 (95% CI 1.54-2.11) low-potency TCS vs non-use: 1.36 (95% CI 1.22-1.51)	Increased risk of lymphoma in patients with AD, especially severe AD. TCS use associated with increased risk for lymphoma. No cases of lymphoma identified in TCI users but number of patients using TCIs was too low to determine OR

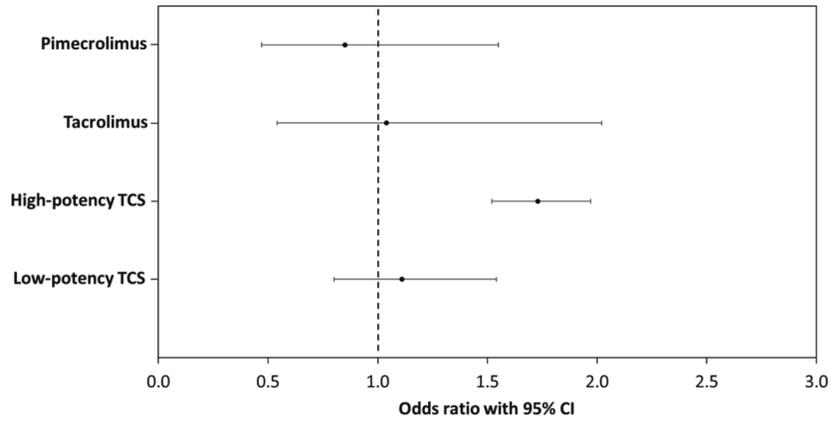
Study	Number of patients	Study design	Results	Conclusion
Hui et al. (2009) (74)	953,064	Retrospective cohort study (US Kaiser Permanente database)	<p>Adjusted HR for cancer: pimecrolimus vs non-use: 1.15 (95% CI 0.99-1.31) tacrolimus vs non-use: 0.93 (95% CI 0.81-1.07)</p> <p>Adjusted HR for T-cell lymphoma: pimecrolimus vs non-use: 2.32 (95% CI 0.89-6.07) tacrolimus vs non-use: 5.44 (95% CI 2.51-11.79)</p>	No increase of overall cancer rate with exposure to tacrolimus or pimecrolimus. No increased risk of T-cell lymphoma with pimecrolimus. Use of tacrolimus may be associated with increased risk of T-cell lymphoma

CI: confidence interval; HR: hazard ratio; OR: odds ratio; RR: relative risk; TCIs: topical calcineurin inhibitors; TCS: topical corticosteroids

Figures

Figure 1. Lymphoma risk in patients with AD treated with TCIs or TCS based on results from a meta-analysis performed by Legendre et al. (2015) (76). TCIs: topical calcineurin inhibitors; TCS: topical corticosteroids CI: confidence interval

A



B

