DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

Atopic dermatitis: a review of topical nonsteroid therapy

Ariana Papier BA[1], Lindsay C Strowd MD[2]

[1]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [2]Department of Dermatology, Wake Forest Baptist Medical Center, Wake Forest University, Winston-Salem, NC, USA

Abstract

Background: Atopic dermatitis is a chronic inflammatory skin condition that affects up to 20% of children and 3% of adults globally. Although topical corticosteroids are considered to be the first-line agents, they can be associated with cutaneous and systemic adverse effects. Since the early 2000s, two new classes of nonsteroid topical therapies, topical calcineurin inhibitors and phosphodiesterase 4 (PDE4) inhibitors, have been introduced and provide a safe treatment alternative.

Method: We performed a search and review of clinical trials that examined the safety and efficacy of topical calcineurin inhibitors and PDE4 inhibitors. The search was conducted using the PubMed database as well as preselected keywords and filters. This review focuses on the safety and efficacy of each therapy.

Results: Sixty-nine clinical trials identified in this study have demonstrated the efficacy and safety of topical calcineurin and a single novel PDE4 inhibitor in the treatment of atopic dermatitis. Topical calcineurin inhibitors have been shown to be effective in both achieving lesion clearance as well as reducing relapse when used long-term and proactively. Similarly, in clinical trials the PDE4 inhibitor showed success in lesion clearance and symptom management. All three therapies (pimecrolimus, tacrolimus, crisaborole) are associated with low systemic absorption. No clinical trials to date have shown an increased risk of systemic adverse events or malignancy such as lymphoma. The most commonly reported treatment-related adverse event across all three therapies was application-site discomfort, pain or pruritus. It is important to note that long-term studies are not yet available for the novel PDE4 inhibitor.

Discussion: Topical calcineurin inhibitors provide a safe and effective alternative to topical corticosteroid use in the treatment of atopic dermatitis. Although the US Food and Drug Administration (FDA) black box warning for topical calcineurin inhibitors remains, studies have not shown an increased risk of malignancy. These warnings have caused a decline in use in favor of topical steroids. A novel PDE4 inhibitor has shown efficacy and safety in studies up to one year. Further long-term safety data is needed.

Keywords: atopic dermatitis, calcineurin inhibitors, crisaborole, eczema, phosphodiesterase 4 inhibitors, pimecrolimus, review, tacrolimus, topical therapy.

Citation

Papier A, Strowd LC. Atopic dermatitis: a review of topical nonsteroid therapy. Drugs in Context 2018; 7: 212521. DOI: 10.7573/dic.212521

Introduction

Atopic dermatitis (AD), an inflammatory skin condition, commonly follows a chronic course associated with periods of remission and relapse. AD is often associated with other atopic diagnoses such as asthma, allergic rhinitis and food allergies [1]. The incidence of AD is high, estimated to be approximately 15–20% of children and 1–3% of adults worldwide [1]. The effect of AD is far-reaching, negatively impacting quality of life as well as causing financial burden for both patients and their families. Pruritus, almost universally present in those suffering with AD, can be severe and has been associated with sleep disturbance. Economic impacts include additional annual doctor visits, medication costs and missed days of work or school [1].

There are currently three classes of US Food and Drug Administration (FDA) approved topical therapies for atopic dermatitis. These include topical steroids, two calcineurin inhibitors and one phosphodiesterase 4 inhibitor (PDE4 inhibitor). Due to the chronic nature of AD it is important that there is an effective and safe treatment that can be used for long-term management. While topical corticosteroids (TCS) have long been considered the first-line therapy, TCS are associated with serious adverse side effects that include skin atrophy, telangiectasia, striae and systemic absorption

affecting the hypothalamic-pituitary-adrenal axis [2,3]. Studies have shown that many patients and caregivers have concerns about TCS use, which has led to a pattern of increased nonadherence [4]. Topical calcineurin inhibitors (TCI), which include pimecrolimus and tacrolimus, have been available since 2000. In 2006, the US FDA attached a black box warning to both drugs based on potential malignancy risk. Since this warning was established, clinical studies have not been able to establish a link between TCI use and increased risk of malignancy [5]. Most recently, a PDE4 inhibitor, crisaborole was FDA approved in 2016 and early studies show an excellent safety profile for the treatment and management of AD.

Method

Search strategy

A search was conducted on nonsteroid topical therapies for the treatment of AD, including tacrolimus, pimecrolimus and crisaborole. The search was performed using the PubMed database using the search 'atopic dermatitis' and 'topical' and ('pimecrolimus' or 'tacrolimus' or 'crisaborole'). Additional literature was selected and reviewed to provide information on the chemical properties, current approved indications or to provide additional analysis on current treatment practices.

Inclusion criteria for studies included (1) English language; (2) available full text; (3) study design of 'clinical study', 'clinical trial', 'clinical trial, Phase I', 'clinical trial, Phase II', 'clinical trial, Phase III', 'clinical trial, Phase IV', 'controlled clinical trial' and 'randomized controlled trial' on PubMed; (4) study size; and (5) drugs studied in relation to AD.

Study selection and data collection

The first search in PubMed using just the keywords given above yielded 656 articles for review. After applying the inclusion criteria and filters listed above, 128 studies were then selected for further review of relevance. Of these articles reviewed, 69 were selected for inclusion. An additional 8 resources were selected during the writing process for a total of 77 resources.

Calcineurin inhibitors

Overview

Topical calcineurin inhibitors, including tacrolimus and pimecrolimus, were FDA approved for the treatment of AD in 2000 and 2001, respectively [6]. TCIs are anti-inflammatory drugs with a lipophilic structure that act by inhibiting the calcineurin phosphatase. This disrupts the activation of T cells and mast cells as well as the transcription and release of inflammatory cytokines [7–9]. Tacrolimus has been shown to impact Langerhans cells while pimecrolimus does not [2,10,11].

In addition to their anti-inflammatory effects, both TCIs have been shown to have additional positive effects on epidermal integrity [12–16]. Tacrolimus use results in improved skin barrier function, skin hydration, and skin thickness in patients with AD [12–15]. Kyllönen and colleagues reported that treatment with 0.1% tacrolimus resulted in a significant increase in collagen synthesis leading to improved skin thickness and reversal of skin atrophy from prior TCS use [12]. Murrell and colleagues reported that in addition to significant clearance of AD lesions, patients treated with pimecrolimus saw a reversal of skin thinning of the neck and head, including the eyelids [16]. These treatments provide a safe alternative to TCS, particularly for treatment of sensitive skin sites such as the head and neck [8,16–19].

Current FDA black box warning

In March 2006, the FDA announced a blanket black box warning for both pimecrolimus and tacrolimus. This notice recommended the use of TCIs only after the failure of other treatments due to a potential increase in risk of malignancies including lymphoma [6]. Additionally, the FDA's Public Health Advisory also released treatment advice that includes using the minimum amount for short-term or intermittent use, in children older than 2 years of age and only in those without a weakened or compromised immune system [6].

This boxed warning was based on a theoretical increase in risk of malignancy including lymphoma [5]. Prior to its topical use in AD, oral and intravenous tacrolimus had been used to suppress the systemic immune system in transplant patients. Malignancies have been associated with oral tacrolimus when used systemically at high concentrations. An animal study with pimecrolimus using a 30× greater exposure than seen with topical use also showed associated malignancy development [5]. These findings were used to support the addition of the black box warning. New malignancies have been reported in patients using topical pimecrolimus or tacrolimus as well. These have been reported by the FDA and by the parent drug manufacturer. Independent experts reviewing these cases found no causal association between topical use of CNI and malignancy. The rate of reported lymphoma in patients exposed to topical tacrolimus is lower than the expected incidence in age-matched controls [20]. No increased risk of malignancy has been seen in recent meta-analyses or the 10-year Pediatric Eczema Elective Registry as of May 2014 [8,21].

Pimecrolimus

Pimecrolimus is a 33-epi-chloro-derivative of the ascomycin macrolactam, which binds to the macrophilin-12 receptor, blocking calcium-dependent activation cascade normally mediated by calcineurin [22]. Pimecrolimus is currently indicated as a second-line therapy for short-term and noncontinuous use in the treatment of mild-to-moderate AD in patients older than 2 years of age [23]. Despite these FDA-approved indications, clinical trials have shown drug

Table 1. Summary of pimecrolimus activity and safety.

Pimecrolimus efficacy compared to control vehicle	Pimecrolimus safety
Significant increase in time between flares	Most common adverse event is application-site pain/burning, mild-to-moderate intensity
Significant reduction in TCS use	Low systemic absorption
Significant increase in number of AD free days	FDA issued black box warning on risk of malignancy
Significant reduction in pruritus	

safety in patients as young as 3 months and in long-term use in patients of all ages [8,24–29].

Clinical trials have demonstrated that pimecrolimus is effective in achieving clearance of AD lesions and associated symptoms as well as for long-term management. Pimecrolimus has a significant steroid-sparing effect, by significantly increasing the time between flares and producing a reduction in days requiring TCS [8,19,24,30–38]. Meurer and colleagues reported a median 144 days before first flare compared with 26 days in the vehicle control in adults with moderate-to-severe AD [37]. In a study with children and adolescents, the difference in AD-free days was also significant averaging 160.2 compared with 137.7 days with 50% fewer relapses overall [30]. Pruritus was shown to be significantly reduced in as early as 48 hours after initiation of treatment [37,39].

A 5-year study of children beginning in infancy supports the efficacy and safety of long-term management of AD with pimecrolimus. Sigurgeirsson and colleagues reported that global successful treatment outcomes were observed in 88.7% of children and in 96.6% of children for facial AD [8]. The association of pimecrolimus treatment with an increased number of disease-free days and reduced need for TCS use (median 7 days) is consistent with a previous trial in infants [24].

Treatment with pimecrolimus is associated with low systemic absorption [2,25,26,29,40–42]. These findings are in line with expectations based on its highly lipophilic structure. In adults with moderate-to-severe AD, Van Leent and colleagues reported that 98% of patients showed systemic levels below the limit of quantification and a maximum measured blood concentration of only 0.8 g/mL after twice daily application [40]. Similarly, trials involving children and infants have demonstrated similar results, with no significant drug accumulation [25,27,29]. Drug absorption remained low even with short-term use four times daily for up to 3 weeks [41]. Pimecrolimus has shown lower systemic absorption compared with tacrolimus [2,42]. Although, it is important to note that generally patients treated with pimecrolimus have milder disease and therefore potentially have less drug exposure [42].

The most frequently reported treatment-related adverse event (TRAE) was application-site pain or burning that was transient [16,18,19,28,30,31,33,36–38,40,43]. In a long-term safety study of adults with moderate-to-severe atopic dermatitis 25.9% of patients reported mild-to-moderate application-site burning [36].

Review of clinical trials and literature shows no significant systemic TRAEs, impairment of systemic immunity or treatment-associated malignancies [8,24–27,29,30,33,36–38, 40,41]. Sigurgeirsson and colleagues reported that normal antibody titers were reported in children treated with pimecrolimus following vaccination (Table 1) [8].

Tacrolimus

Tacrolimus is a macrolide molecule that binds to the FKBP-12 protein and inhibits normal activation of calcineurin phosphatase activity. This results in a decrease in cytokine production and downstream decrease in T-lymphocyte activation. Tacrolimus has been isolated from *Streptomyces tsukubaensis* bacterial strain [25]. Tacrolimus is available in both 0.03 and 0.1% ointment formulations for the short-term and intermittent treatment of moderate-to-severe AD in adults and children >2 years of age [44].

Similar to pimecrolimus, tacrolimus has been shown to be safe and effective over longer treatment periods and in children less than 2 years of age. Clinical trials have shown both concentrations of tacrolimus are safe and effective in treating AD for short and long-term use, including in sensitive skin areas such as the head and neck [45–57]. Tacrolimus 0.1% has shown superior efficacy in treating children and adults with more severe AD versus 0.03% tacrolimus as well as pimecrolimus [43,53,58]. While tacrolimus is effective in treating AD, there are conflicting findings in comparing tacrolimus to traditional TCS. In a Phase III trial, Reitamo and colleagues reported that by month 3, significantly more patients in the 0.1% tacrolimus arm had seen a response to treatment (72.6%) compared with those treated with 0.1% hydrocortisone butyrate (52.3%). Patients treated with tacrolimus continued to see superior results in terms of skin healing and AD symptoms at every point over the 6-month study [59]. Similar findings were seen by Reitamo and colleagues comparing tacrolimus 0.03% and 0.1–1% hydrocortisone acetate in the pediatric population as well as Doss and colleagues comparing tacrolimus 0.1% to fluticasone 0.005% for facial AD [17,51,58]. However, in a trial completed by Bieber and colleagues methylprednisolone aceponate 0.1% showed superior efficacy compared to tacrolimus 0.03% in children [47]. Additional studies have shown that while both

Table 2. Summary of tacrolimus efficacy and safety.

Tacrolimus efficacy	Tacrolimus safety
Superior efficacy at 0.1% concentration over tacrolimus 0.03% and pimecrolimus 1%	Most common adverse event is application-site pain/burning, mild-to-moderate intensity
Conflicting studies on efficacy compared to topical corticosteroid (CS) use	Low systemic absorption
Significant improvement in time between flares compared to vehicle control	FDA issued black box warning on risk of malignancy
Significant reduction in number of disease flares compared to vehicle control	

treatments are effective, there are no statistical differences overall [46,51,60]. It is important to note that findings in comparative studies are limited by low potency steroids and varying degrees of disease severity [51,61].

As with pimecrolimus, long-term trials have shown the potential of tacrolimus to be used proactively to sustain disease improvement and reduce recurrences while maintaining a high safety profile [59,62–65]. Wollenberg and colleagues reported that twice-weekly proactive treatment (0.1%) in adults was significant in reducing the severity and time until exacerbation with a mean 142 days before first exacerbation compared to 15 days in those treated reactively [62]. In the pediatric population, tacrolimus 0.03% applied to healthy-appearing but affected skin reduced the number and severity of relapses [64]. Paller and colleagues reported consistent findings, but that significantly more patients treated with TCS (first 4 days) prior to tacrolimus had results of 'clear' or 'almost clear' at study end than with tacrolimus alone [66].

Across all clinical trials reviewed, the most commonly reported TRAE was application-site irritation including pain, burning, stinging and pruritus [15–18,21,43,47–49,51,54,55,57–71]. Application-site reactions were commonly described as mild-to-moderate and transient. Burning with application may be due to the vehicle contents of TCIs. Transient nature of application-site discomfort is attributed to lesion healing and increased skin thickness [59,72].

Pharmacokinetic studies show low systemic absorption, consistent with expectations of a topical lipophilic drug. In a Phase I trial of patients >5 years of age, Alaiti and colleagues reported that topical tacrolimus 0.3% was associated with low systemic absorption and no significant accumulation [67]. Follow-up studies of tacrolimus 0.03 and 0.1% report consistent findings in both adults and children, with low systemic absorption that decreases over time as lesions improve [45,50,52,55–57,67,73].

No clinical trials reviewed reported treatment-related malignant neoplasms or significant treatment-related laboratory changes over time [17,45,49,51,52,54–59,61,64,65,67–70,72]. Hofman and colleagues cite normal antibody titers following vaccination in children treated with tacrolimus, helping to reduce systemic immunity concerns [68]. Additionally, Kang and colleagues reported that there was no growth restriction in children 2–15 years treated with tacrolimus over 12 months [54].

Although not yet FDA approved for use in children <2 years of age, long-term studies of tacrolimus 0.03% have been completed and report similar findings to studies conducted in older children [71,72]. A Phase II trial completed over 2 years concluded that tacrolimus 0.03% was effective with 63.3% of patients evaluated as 'clear' or 'excellent response' at study conclusion [71]. In a pharmacokinetic study, Reitamo and colleagues reported low systemic exposure and skin concentrations that decreased with increased skin thickness [72]. TRAEs in both trials included minor infections and application-site irritation, consistent with studies of older children and adults (Table 2).

PDE4 Inhibitor

Crisaborole 2%

Crisaborole is a benzoxaborole compound whose central boron atom has the ability to bind to the bimetal center of the PDE4 enzyme, thereby inhibiting normal PDE4 activity. PDE4 inhibitors suppress cytokine production and inhibit reactive oxygen species production [74,75]. It is the latest topical anti-inflammatory treatment to be FDA approved for the treatment of atopic dermatitis in both children and adults. Crisaborole 2% topical ointment is indicated in adults and children over 2 years of age with mild-to-moderate atopic dermatitis [76].

Clinical trials have shown that crisaborole is effective in improving both AD lesions and associated symptoms. Paller and colleagues reported that crisaborole 2% ointment was efficacious with 51.7 and 48.5% of patients achieving scores of 'clear' or 'almost clear' during dual Phase III trials [77]. Trials have also shown significant improvement in AD symptoms including erythema, excoriation, exudation, lichenification and pruritus [74,77]. The earlier Phase Ib trial showed tolerability in sensitive skin areas including the genitalia, intertriginous areas, face and hairline, where treatment with topical corticosteroids is often avoided [78].

Crisaborole has been found to be well-tolerated with limited reported adverse events. Across all clinical trials, the most common TRAE was application-site pain, burning or stinging. In dual Phase III trials, Paller and colleagues reported that 94.3% of TRAEs were considered mild to moderate, with most application-site discomfort resolving within 1 day of application [77]. Findings were consistent with previous studies [75,78–80]. Eichenfield and colleagues demonstrated through

Table 3. Summary of crisaborole efficacy and safety.

Crisaborole efficacy compared to vehicle control	Crisaborole safety
Significant improvement in investigator global assessment	Most common adverse event is application-site pain/burning, mild-to-moderate intensity
Significant improvement in pruritus	Low systemic absorption
Well-tolerated in intertriginous skin and facial skin	No black box warning regarding malignancy

a 48-week extension that crisaborole has a favorable long-term safety profile without increasing risk for TRAEs [76]. Researchers expressed confidence in the application of these results as a significant amount of ointment (~133 g/patient/month) was used by each patient throughout each treatment period over the 48-week trial [76].

No serious TRAEs, deaths or significant measured changes in laboratory values or vital signs have been reported [75–80]. Systemic exposure of both crisaborole and its metabolite (AN7603) were found to be limited during its maximal use study [75]. Eichenfield and colleagues found no increasing incidence of neoplasms or infections associated with the long-term use of treatment [76].

Ciaravino and colleagues investigated the long-term carcinogenicity of high-dose oral and topical crisaborole in rats and mice respectively. Topical application to animals was not associated with adverse effects. Crisaborole was found to be nontumorigenic in mice and male rats. While large doses of 300 mg/kg/day of oral therapy was shown to increase the incidence of benign granular cell tumors in the reproductive tract of female rat, it was nontumorigenic at 100 mg/kg/day or 1× human safety levels. Researchers considered human-relevance of these benign granular tumors to be low (Table 3) [81].

Discussion

Atopic dermatitis is a chronic inflammatory cutaneous disease that affects a large portion of the population both here in the United States as well as globally. Due to the chronic and recurring nature of the disease, effective and safe drugs are needed that can be used for long-term disease management.

The mainstay of treatment in the management of AD is TCS. However, long-term use of TCS may be associated with severe systemic and cutaneous adverse reactions, especially if used improperly. Knowledge of these risks has been shown to increase patient nonadherence. Pimecrolimus and tacrolimus are currently considered second-line options for AD due the FDA black box warning that is based on a theoretical increased risk of malignancy [5,7]. Although many studies have shown that long-term use of tacrolimus and pimecrolimus is effective with a favorable safety profile and low systemic absorption, the black box warning has remained in place. In comparing TCIs, tacrolimus has been shown to be more effective than pimecrolimus with similar safety profile [43]. However, these warnings have led to a decline in their use in adults and children and their off-label use in infants. A recent systematic review by Siegfried and colleagues of clinical trials and meta-analyses have not shown a significant increased risk of malignancy with TCI use [21].

The approval of crisaborole in 2016 has provided an additional alternative to TCS in the treatment of AD. Completed safety trials have demonstrated that crisaborole can be used safely with minimal side effects for over a year, however longer safety data is not yet available due to the novelty of this topical agent [76].

Disclosure and potential conflicts of interest: The authors have nothing to disclose. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at: http://www.drugsincontext.com/wp-content/uploads/2018/03/dic.212521-COI.pdf

Article URL: http://www.drugsincontext.com/atopic-dermatitis-a-review-of-topical-nonsteroid-therapy

Correspondence: Lindsay Strowd, Wake Forest University School of Medicine, Winston-Salem, NC, USA. lchaney@wakehealth.edu

Provenance: invited; externally peer reviewed.

Submitted: 6 December 2017; **Peer review comments to author:** 23 February 2018; **Revised manuscript received:** 28 February 2018; **Accepted:** 2 March 2018; **Publication date:** 3 April 2018.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

For all manuscript and submissions enquiries, contact the Editorial office dic.editorial@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Avena-Woods C. Overview of atopic dermatitis. Am J Manag Care. 2017;23(8 Suppl):S115–23. PubMed PMID: 28978208
2. Stuetz A, Baumann K, Grassberger M, Wolff K, Meingassner JG. Discovery of topical calcineurin inhibitors and pharmacological profile of pimecrolimus. Int Arch Allergy Immunol. 2006;141(3):199–212. http://dx.doi.org/10.1159/000095289
3. Aschoff R, Schmitt J, Knuschke P, Koch E, Bräutigam M, Meurer M. Evaluation of the atrophogenic potential of hydrocortisone 1% cream and pimecrolimus 1% cream in uninvolved forehead skin of patients with atopic dermatitis using optical coherence tomography. Exp Dermatol. 2011;20(10):832–6. http://dx.doi.org/10.1111/j.1600-0625.2011.01335.x
4. Li AW, Yin ES, Antaya RJ. Topical corticosteroid phobia in atopic dermatitis: a systematic review. JAMA Dermatol. 2017;153(10):1036–42. http://dx.doi.org/10.1001/jamadermatol.2017.2437
5. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. Am J Clin Dermatol. 2013;14(3):163–78. http://dx.doi.org/10.1007/s40257-013-0020-1
6. Public Health Advisory: Elidel (pimecrolimus) Cream and protopic (tacrolimus) ointment. Postmarket Drug Safety Information for Patients and Providers. Center for Drug Evaluation and Research. Available at https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051760.htm [Last accessed 20 November 2017].
7. Carr WW. Topical calcineurin inhibitors for atopic dermatitis: review and treatment recommendations. Paediatr Drugs. 2013;15(4):303–10. http://dx.doi.org/10.1007/s40272-013-0013-9
8. Sigurgeirsson B, Boznanski A, Todd G, Vertruyen A, Schuttelaar M-LA, Zhu X, Schauer U, Qaqundah P, Poulin Y, Kristjansson S, von Berg A, Nieto A, Boguniewicz M, Paller AS, Dakovic R, Ring J, Luger T. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. Pediatrics. 2015;135(4):597–606. http://dx.doi.org/10.1542/peds.2014-1990
9. Caproni M, Torchia D, Antiga E, Terranova M, Volpi W, del Bianco E, D'Agata A, Fabbri P. The comparative effects of tacrolimus and hydrocortisone in adult atopic dermatitis: an immunohistochemical study. Br J Dermatol. 2007;156(2):312–9. http://dx.doi.org/10.1111/j.1365-2133.2006.07609.x
10. Hoetzenecker W, Ecker R, Kopp T, Stuetz A, Stingl G, Elbe-Bürger A. Pimecrolimus leads to an apoptosis-induced depletion of T cells but not Langerhans cells in patients with atopic dermatitis. J Allergy Clin Immunol. 2005;115(6):1276–83. http://dx.doi.org/10.1016/j.jaci.2005.02.011
11. Wollenberg A, Sharma S, von Bubnoff D, Geiger E, Haberstok J, Bieber T. Topical tacrolimus (FK506) leads to profound phenotypic and functional alterations of epidermal antigen-presenting dendritic cells in atopic dermatitis. J Allergy Clin Immunol. 2001;107(3):519–25. http://dx.doi.org/10.1067/mai.2001.112942
12. Kyllönen H, Remitz A, Mandelin JM, Elg P, Reitamo S. Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. Br J Dermatol. 2004;150(6):1174–81. http://dx.doi.org/10.1111/j.1365-2133.2004.06017.x
13. Danby SG, Chittock J, Brown K, Albenali LH, Cork MJ. The effect of tacrolimus compared with betamethasone valerate on the skin barrier in volunteers with quiescent atopic dermatitis. Br J Dermatol. 2014;170(4):914–21. http://dx.doi.org/10.1111/bjd.12778
14. Dähnhardt-Pfeiffer S, Dähnhardt D, Buchner M, Walter K, Proksch E, Fölster-Holst R. Comparison of effects of tacrolimus ointment and mometasone furoate cream on the epidermal barrier of patients with atopic dermatitis. J Dtsch Dermatol Ges. 2013;11(5):437–43. http://dx.doi.org/10.1111/ddg.12074
15. Chittock J, Brown K, Cork MJ, Danby SG. Comparing the effect of a twice-weekly tacrolimus and betamethasone valerate dose on the subclinical epidermal barrier defect in atopic dermatitis. Acta Derm Venereol. 2015;95:653–8. http://dx.doi.org/10.2340/00015555-2048
16. Murrell DF, Calvieri S, Ortonne JP, Ho VC, Weise-Riccardi S, Barbier N, Paul CF. A randomized controlled trial of pimecrolimus cream 1% in adolescents and adults with head and neck atopic dermatitis and intolerant of, or dependent on, topical corticosteroids. Br J Dermatol. 2007;157(5):954–9. http://dx.doi.org/10.1111/j.1365-2133.2007.08192.x
17. Doss N, Reitamo S, Dubertret L, Fekete GL, Kamoun M-R, Lahfa M, Ortonne J-P. Superiority of tacrolimus 0·1% ointment compared with fluticasone 0·005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. Br J Dermatol. 2009;161(2):427–34. http://dx.doi.org/10.1111/j.1365-2133.2009.09143.x
18. Hoeger PH, Lee K-H, Jautova J, Wohlrab J, Guettner A, Mizutani G, Hultsch T. The treatment of facial atopic dermatitis in children who are intolerant of, or dependent on, topical corticosteroids: a randomized, controlled clinical trial. Br J Dermatol. 2009;160(2):415–22. http://dx.doi.org/10.1111/j.1365-2133.2008.08928.x

19. Zuberbier T, Bräutigam M. Long-term management of facial atopic eczema with pimecrolimus cream 1% in paediatric patients with mild to moderate disease. J Eur Acad Dermatol Venereol. 2008;22(6):718–21. http://dx.doi.org/10.1111/j.1468-3083.2008.02586.x
20. Ormerod AD. Topical tacrolimus and pimecrolimus and the risk of cancer: how much cause for concern? Br J Dermatol. 153(4):1365-2133. http://dx.doi.org/10.1111/j.1365-2133.2005.06899.x
21. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. BMC Pediatr. 2016;16:75. http://dx.doi.org/10.1186/s12887-016-0607-9
22. National Center for Biotechnology Information. PubChem Compound Database; CID=6509979. Available at https://pubchem.ncbi.nlm.nih.gov/compound/6509979 [Last accessed 28 February 2018].
23. Elidel (pimecrolimus) Cream 1% – prescribing information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021302s011lbl.pdf [Last accessed 13 March 2018].
24. Kapp A, Papp K, Bingham A, Fölster-Holst R, Ortonne J-P, Potter PC, Gulliver W, Paul C, Molloy S, Barbier N, Thurston M, de Prost Y, Flare Reduction in Eczema with Elidel (infants) multicenter investigator study group. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol. 2002;110(2):277–84. PubMed PMID: 12170269
25. National Center for Biotechnology Information. PubChem Compound Database; CID=445643. Available at https://pubchem.ncbi.nlm.nih.gov/compound/445643 [Last accessed 28 February 2018].
26. Eichenfield LF, Ho V, Matsunaga J, Leclerc P, Paul C, Hanifin JM. Blood concentrations, tolerability and efficacy of pimecrolimus cream 1% in Japanese infants and children with atopic dermatitis. J Dermatol. 2007;34(4):231–6. http://dx.doi.org/10.1111/j.1346-8138.2007.00259.x
27. Lakhanpaul M, Davies T, Allen BR, Schneider D. Low systemic exposure in infants with atopic dermatitis in a 1-year pharmacokinetic study with pimecrolimus cream 1%*. Exp Dermatol. 2006;15(2):138–41. http://dx.doi.org/10.1111/j.1600-0625.2006.00398.x
28. Eichenfield LF, Lucky AW, Boguniewicz M, Langley RGB, Cherill R, Marshall K, Bush C, Graeber M. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol. 2002;46(4):495–504. PubMed PMID: 11907497
29. Harper J, Green A, Scott G, Gruendl E, Dorobek B, Cardno M, Burtin P. First experience of topical SDZ ASM 981 in children with atopic dermatitis. Br J Dermatol. 2001;144(4):781–7. PubMed PMID: 11298537
30. Sigurgeirsson B, Ho V, Ferrándiz C, Andriano K, Grinienko A, Jimenez P, Pimecrolimus 1% cream in (paediatric) Eczema: Prevention of Progression multi-centre investigator study group. Effectiveness and safety of a prevention-of-flare-progression strategy with pimecrolimus cream 1% in the management of paediatric atopic dermatitis. J Eur Acad Dermatol Venereol. 2008;22(11):1290–301. http://dx.doi.org/10.1111/j.1468-3083.2008.02785.x
31. Gollnick H, Kaufmann R, Stough D, Heikkila H, Andriano K, Grinienko A, Jimenez P, Pimecrolimus Cream 1% in (adult) Eczema: Prevention of Progression Multicentre Investigator Study Group. Pimecrolimus cream 1% in the long-term management of adult atopic dermatitis: prevention of flare progression. A randomized controlled trial. Br J Dermatol. 2008;158(5):1083–93. http://dx.doi.org/10.1111/j.1365-2133.2008.08484.x
32. Ring J, Abraham A, de Cuyper C, Kim K, Langeland T, Parra V, Pigatto P, Reunala T, Szczepanski R, Möhrenschlager M, Bräutigam M, Rossi AB, Meents-Kopecky E, Schneider D. Control of atopic eczema with pimecrolimus cream 1% under daily practice conditions: results of a > 2000 patient study. J Eur Acad Dermatol Venereol. 2008;22(2):195–203. http://dx.doi.org/10.1111/j.1468-3083.2007.02368.x
33. Zuberbier T, Heinzerling L, Bieber T, Schauer U, Klebs S, Bräutigam M. Steroid-sparing effect of pimecrolimus cream 1% in children with severe atopic dermatitis. Dermatology. 2007;215(4):325–30. http://dx.doi.org/10.1159/000107627
34. Lübbe J, Friedlander SF, Cribier B, Morren M-A, García-Díez A, Gelmetti C, Hofmann H, Houwing RH, Kownacki S, Langley RGB, Virtanen M, Wolff K, Wisseh S, McGeown C, Abrams B, Schneider D, NOBEL (New Online Based ELidel) Study Group. Safety, efficacy, and dosage of 1% pimecrolimus cream for the treatment of atopic dermatitis in daily practice. Am J Clin Dermatol. 2006;7(2):121–31. PubMed PMID: 16605292
35. Papp K, Staab D, Harper J, Potter P, Puig L, Ortonne J-P, Molloy S, Barbier N, Paul C, Multicentre Investigator Study Group. Effect of pimecrolimus cream 1% on the long-term course of pediatric atopic dermatitis. Int J Dermatol. 2004;43(12):978–83. http://dx.doi.org/10.1111/j.1365-4632.2004.02121.x
36. Luger TA, Lahfa M, Fölster-Holst R, Gulliver WP, Allen R, Molloy S, Barbier N, Paul C, Bos JD. Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis. J Dermatolog Treat. 2004;15(3):169–78. https://doi.org/10.1080/09546630410033781
37. Meurer M, Fartasch M, Albrecht G, Vogt T, Worm M, Ruzicka T, Altmeyer PJ, Schneider D, Weidinger G, Braeutigam M, CASM-DE-01 Study Group. Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis. Dermatology. 2004;208(4):365–72. http://dx.doi.org/10.1159/000078462

38. Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A, Dobozy A, Paul C, Molloy S, Hultsch T, Graeber M, Cherill R, de Prost Y, Flare Reduction in Eczema with Elidel (Children) Multicenter Investigator Study Group. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics. 2002;110(1 Pt 1):e2. PubMed PMID: 12093983
39. Kaufmann R, Bieber T, Helgesen AL, Andersen BL, Luger T, Poulin Y, Al-Hafidh J, Paul C, multicentre investigator group. Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial. Allergy. 2006;61(3):375–81. http://dx.doi.org/10.1111/j.1398-9995.2005.00977.x
40. Van Leent EJM, De Vries HJC, Ebelin M, Burtin P, Scott G, Bos JD. Blood concentrations of pimecrolimus in adult patients with atopic dermatitis following intermittent administration of pimecrolimus cream 1% (Elidel®) for up to 1 year. J Dermatolog Treat. 2007;18(1):19–22. https://doi.org/10.1080/09546630601121037
41. Ling M, Gottlieb A, Pariser D, Caro I, Stewart D, Scott G, Abrams K. A randomized study of the safety, absorption and efficacy of pimecrolimus cream 1% applied twice or four times daily in patients with atopic dermatitis. J Dermatolog Treat. 2005;16(3):142–8. http://dx.doi.org/10.1080/09546630510033159
42. Draelos Z, Nayak A, Pariser D, Shupack JL, Chon K, Abrams B, Paul CF. Pharmacokinetics of topical calcineurin inhibitors in adult atopic dermatitis: a randomized, investigator-blind comparison. J Am Acad Dermatol. 2005;53(4):602–9. http://dx.doi.org/10.1016/j.jaad.2005.06.013
43. Kirsner RS, Heffernan MP, Antaya R. Safety and efficacy of tacrolimus ointment versus pimecrolimus cream in the treatment of patients with atopic dermatitis previously treated with corticosteroids. Acta Derm Venereol. 2010;90(1):58–64. http://dx.doi.org/10.2340/00015555-0748
44. Medication Guide – Protopic (tacrolimus) Ointment 0.03%, Ointment 0.1%. Available at https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM107848.pdf [Last accessed 13 March 2018].
45. Undre NA, Moloney FJ, Ahmadi S, Stevenson P, Murphy GM. Skin and systemic pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2009;160(3):665–9. http://dx.doi.org/10.1111/j.1365-2133.2008.08974.x
46. Neumann E, Amtage D, Bruckner-Tuderman L, Mockenhaupt M. A single-center open-label long-term comparison of tacrolimus ointment and topical corticosteroids for treatment of atopic dermatitis. J Dtsch Dermatol Ges. 2008;6(7):548–53. http://dx.doi.org/10.1111/j.1610-0387.2008.06641.x
47. Bieber T, Vick K, Fölster-Holst R, Belloni-Fortina A, Städtler G, Worm M, Arcangeli F. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. Allergy. 2007;62(2):184–9. http://dx.doi.org/10.1111/j.1398-9995.2006.01269.x
48. Schachner LA, Lamerson C, Sheehan MP, Boguniewicz M, Mosser J, Raimer S, Shull T, Jaracz E, US Tacrolimus Ointment Study Group. Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: results from a randomized, double-blind, vehicle-controlled study. Pediatrics. 2005;116(3):e334–42. http://dx.doi.org/10.1542/peds.2004-2638
49. Tan J, Langley R. Safety and efficacy of tacrolimus ointment 0.1% (Protopic) in atopic dermatitis: a Canadian open-label multicenter study. J Cutan Med Surg. 2004;8(4):213–9. http://dx.doi.org/10.1177/120347540400800402
50. Rubins A, Gutmane R, Valdmane N, Stevenson P, Foster C, Undre N. Pharmacokinetics of 0.1% tacrolimus ointment after first and repeated application to adults with moderate to severe atopic dermatitis. J Invest Dermatol. 2005;125(1):68–71. http://dx.doi.org/10.1111/j.0022-202X.2005.23754.x
51. Reitamo S, Harper J, Bos JD, Cambazard F, Bruijnzeel-Koomen C, Valk P, Smith C, Moss C, Dobozy A, Palatsi R, The European Tacrolimus Ointment Group. 0·03% tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized double-blind controlled trial. Br J Dermatol. 2004;150(3):554–62. http://dx.doi.org/10.1046/j.1365-2133.2004.05782.x
52. Harper J, Smith C, Rubins A, Green A, Jackson K, Zigure S, Bourke J, Alomar A, Stevenson P, Foster C, Undre N. A multicenter study of the pharmacokinetics of tacrolimus ointment after first and repeated application to children with atopic dermatitis. J Invest Dermatol. 2005;124(4):695–9. http://dx.doi.org/10.1111/j.0022-202X.2005.23644.x
53. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. J Am Acad Dermatol. 2001;44(1 Suppl):S28–38. PubMed PMID: 11145793
54. Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol. 2001;44(1 Suppl):S58–64. PubMed PMID: 11145796
55. Reitamo S, Wollenberg A, Schöpf E, Perrot JL, Marks R, Ruzicka T, Christophers E, Kapp A, Lahfa M, Rubins A, Jablonska S, Rustin M. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. Arch Dermatol. 2000;136(8):999–1006. https://jamanetwork.com/journals/jamadermatology/fullarticle/190519

56. Boguniewicz M, Fiedler VC, Raimer S, Lawrence ID, Leung DY, Hanifin JM. A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. Pediatric Tacrolimus Study Group. J Allergy Clin Immunol. 1998;102(4 Pt 1):637–44. PubMed PMID: 9802373
57. Ruzicka T, Bieber T, Schöpf E, Rubins A, Dobozy A, Bos JD, Jablonska S, Ahmed I, Thestrup-Pedersen K, Daniel F, Finzi A, Reitamo S. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. N Engl J Med. 1997;337(12):816–21. http://dx.doi.org/10.1056/NEJM199709183371203
58. Reitamo S, Van Leent EJM, Ho V, Harper J, Ruzicka T, Kalimo K, Cambazard F, Rustin M, Taïeb A, Gratton D, Sauder D, Sharpe G, Smith C, Jünger M, de Prost Y, European /Canadian Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. J Allergy Clin Immunol. 2002;109(3):539–46. PubMed PMID: 11898004
59. Reitamo S, Ortonne JP, Sand C, Cambazard F, Bieber T, Fölster-Holst R, Vena G, Bos JD, Fabbri P, Groenhoej Larsen C, the European Tacrolimus Ointment Study Group. A multicentre, randomized, double-blind, controlled study of long-term treatment with 0·1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2005;152(6):1282–9. http://dx.doi.org/10.1111/j.1365-2133.2005.06592.x
60. Mandelin J, Remitz A, Virtanen H, Reitamo S. One-year treatment with 0.1% tacrolimus ointment versus a corticosteroid regimen in adults with moderate to severe atopic dermatitis: A randomized, double-blind, comparative trial. Acta Derm Venereol. 2010;90(2):170–4. http://dx.doi.org/10.2340/00015555-0803
61. Reitamo S, Ortonne J-P, Sand C, Bos J, Cambazard F, Bieber T, Grønhøj-Larsen C, Rustin M, Fölster-Holst R, Schuttelaar M, European Tacrolimus Ointment Study Group. Long-term treatment with 0.1% tacrolimus ointment in adults with atopic dermatitis: results of a two-year, multicentre, non-comparative study. Acta Derm Venereol. 2007;87(5):406–12. http://dx.doi.org/10.2340/00015555-0282
62. Wollenberg A, Reitamo S, Girolomoni G, Lahfa M, Ruzicka T, Healy E, Giannetti A, Bieber T, Vyas J, Deleuran M, European Tacrolimus Ointment Study Group. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy. 2008;63(7):742–50. PubMed PMID: 18592619
63. Thaci D, Chambers C, Sidhu M, Dorsch B, Ehlken B, Fuchs S. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: clinical efficacy and economic impact over 12 months. J Eur Acad Dermatol Venereol. 2010;24(9):1040–6. http://dx.doi.org/10.1111/j.1468-3083.2010.03577.x
64. Thaçi D, Reitamo S, Gonzalez Ensenat MA, Moss C, Boccaletti V, Cainelli T, Van Der Valk P, Buckova H, Sebastian M, Schuttelaar ML, Ruzicka T, for the European Tacrolimus Ointment Study Group. Proactive disease management with 0·03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. Br J Dermatol. 2008;159(6):1348–56. http://dx.doi.org/10.1111/j.1365-2133.2008.08813.x
65. Breneman D, Fleischer AB Jr, Abramovits W, Zeichner J, Gold MH, Kirsner RS, Shull TF, Crowe AW, Jaracz E, Hanifin JM, Tacrolimus Ointment Study Group. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. J Am Acad Dermatol. 2008;58(6):990–9. http://dx.doi.org/10.1016/j.jaad.2008.02.008
66. Paller AS, Eichenfield LF, Kirsner RS, Shull T, Jaracz E, Simpson EL, US Tacrolimus Ointment Study Group. Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis: a new paradigm for use. Pediatrics. 2008;122(6):e1210–8. http://dx.doi.org/10.1542/peds.2008-1343
67. Alaiti S, Kang S, Fiedler VC, Ellis CN, Spurlin DV, Fader D, Ulyanov G, Gadgil SD, Tanase A, Lawrence I, Scotellaro P, Raye K, Bekersky I. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. J Am Acad Dermatol. 1998;38(1):69–76. PubMed PMID: 9448208
68. Hofman T, Cranswick N, Kuna P, Boznanski A, Latos T, Gold M, Murrell DF, Gebauer K, Behre U, Machura E, Olafsson J, Szalai Z, International Tacrolimus Ointment Study Group. Tacrolimus ointment does not affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children. Arch Dis Child. 2006;91(11):905–10. http://dx.doi.org/10.1136/adc.2006.094276
69. Naylor M, Elmets C, Jaracz E, Rico JM. Non-melanoma skin cancer in patients with atopic dermatitis treated with topical tacrolimus. J Dermatolog Treat. 2005;16(3):149–53. http://www.tandfonline.com/doi/abs/10.1080/09546630510041088
70. Reitamo S, Rustin M, Ruzicka T, Cambazard F, Kalimo K, Friedmann PS, Schoepf E, Lahfa M, Diepgen TL, Judodihardjo H, Wollenberg A, Berth-Jones J, Bieber T, European Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. J Allergy Clin Immunol. 2002;109(3):547–55. PubMed PMID: 11898005
71. Mandelin JM, Rubins A, Remitz A, Cirule K, Dickinson J, Ho V, Mäkelä MJ, Rubins S, Reitamo S, Undre N. Long-term efficacy and tolerability of tacrolimus 0.03% ointment in infants:* a two-year open-label study. Int J Dermatol. 2012;51(1):104–10. http://dx.doi.org/10.1111/j.1365-4632.2011.05015.x

72. Reitamo S, Mandelin J, Rubins A, Remitz A, Mäkelä M, Cirule K, Rubins S, Zigure S, Ho V, Dickinson J, Undre N. The pharmacokinetics of tacrolimus after first and repeated dosing with 0.03% ointment in infants with atopic dermatitis. Int J Dermatol. 2009;48(4):348–55. http://dx.doi.org/10.1111/j.1365-4632.2009.03853.x
73. Krueger GG, Eichenfield L, Goodman JJ, Krafchik BR, Carlin CS, Pang M-L, Croy R, Holum ME, Jaracz E, Sawamoto T, Keirns J. Pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adult and pediatric patients with moderate to severe atopic dermatitis. J Drugs Dermatol. 2007;6(2):185–93. PubMed PMID: 17373177
74. National Center for Biotechnology Information. PubChem Compound Database; CID=44591583. Available at https://pubchem.ncbi.nlm.nih.gov/compound/44591583 [Last accessed 28 February 2018].
75. Zane LT, Kircik L, Call R, Tschen E, Draelos ZD, Chanda S, Van Syoc M, Hebert AA. Crisaborole topical ointment, 2% in patients ages 2 to 17 years with atopic dermatitis: a phase 1b, open-label, maximal-use systemic exposure study. Pediatr Dermatol. 2016;33(4):380–7. http://dx.doi.org/10.1111/pde.12872
76. Eichenfield LF, Call RS, Forsha DW, Fowler J Jr, Hebert AA, Spellman M, Stein Gold LF, Van Syoc M, Zane LT, Tschen E. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. J Am Acad Dermatol. 2017;77(4):641–9.e5. http://dx.doi.org/10.1016/j.jaad.2017.06.010
77. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, Spellman MC, Stein Gold LF, Zaenglein AL, Hughes MH, Zane LT, Hebert AA. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol. 2016;75(3):494–503.e6. http://dx.doi.org/10.1016/j.jaad.2016.05.046
78. Zane LT, Hughes MH, Shakib S. Tolerability of crisaborole ointment for application on sensitive skin areas: a randomized, double-blind, vehicle-controlled study in healthy volunteers. Am J Clin Dermatol. 2016;17(5):519–26. http://dx.doi.org/10.1007/s40257-016-0204-6
79. Murrell DF, Gebauer K, Spelman L, Zane LT. Crisaborole topical ointment, 2% in adults with atopic dermatitis: a phase 2a, vehicle-controlled, proof-of-concept study. J Drugs Dermatol. 2015;14(10):1108–12. http://jddonline.com/articles/dermatology/S1545961615P1108X
80. Stein Gold LF, Spelman L, Spellman MC, Hughes MH, Zane LT. A phase 2, randomized, controlled, dose-ranging study evaluating crisaborole Topical ointment, 0.5% and 2% in adolescents with mild to moderate atopic dermatitis. J Drugs Dermatol. 2015;14(12):1394–9. http://jddonline.com/articles/dermatology/S1545961615P1394X
81. Ciaravino V, Coronado D, Lanphear C, Chanda S. 2-Year animal carcinogenicity results for crisaborole, a novel phosphodiesterase 4 inhibitor for atopic dermatitis. J Dermatol Sci. 2017;87(2):116–22. http://dx.doi.org/10.1016/j.jdermsci.2017.03.020