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Topical Agents for the Treatment of Atopic Dermatitis

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ABSTRACT

Approval of the new topical phosphodiesterase 4 inhibitor crisaborole ointment, 2%, to treat mild-to-moderate atopic dermatitis (AD) warrants careful consideration of available efficacy and safety data for topical therapies to contribute to a better understanding of the role of crisaborole in the treatment of mild-to-moderate AD. A literature review was conducted to identify results of randomized, blinded, vehicle-controlled trials of topical agents for the treatment of AD published from January 1, 1997 to April 30, 2018. This review summarizes the efficacy and safety data of topical therapies including corticosteroids, calcineurin inhibitors, and crisaborole and it shows that comparison among available agents is difficult because of differing methodologies used across clinical trials and that there is considerable variability in safety reporting among AD trials. Published clinical studies for crisaborole demonstrate its efficacy and manageable safety profile.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease that follows a chronic and relapsing course.[1] Essential features include pruritus and eczematous lesions that present with a typical morphology and age-associated distribution.[2,3] Up to 90% of children with AD have mild or moderate disease.[4] Common signs and symptoms include pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification, which vary by age and chronicity of lesions.[2] Because of the chronicity, intense symptom burden, and visible nature of the disease, patients with AD frequently have reduced quality of life (QoL) and psychological comorbidities, including depression and anxiety.[5] Pruritus is responsible for a significant portion of this burden, which includes the associated impact on sleep quality.[2,6]

According to the American Academy of Dermatology (2014) and joint guidelines of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology (2013), topical therapies remain standard treatment for AD and provide efficacy while minimizing the potential for systemic adverse events (AEs).[7,8] Basic skin care, moisturizers, and trigger avoidance are recommended as initial treatment and are integral to AD therapy, aiming to treat and prevent xerosis, reduce transepidermal water loss (TEWL), reduce signs of AD, and prevent flares.[7,8] When the AD is not sufficiently controlled with nonpharmacologic approaches, topical corticosteroids (TCSs) are recommended.[7,8] TCSs have been the mainstay of anti-inflammatory therapy for AD for decades and can be used reactively to treat established lesions and proactively to prevent relapse.[7] However, safety concerns regarding local and systemic AEs can result in treatment hesitancy in caregivers and patients.[7,9] Therefore, appropriate selection of TCS potency, correct application (including duration and location of treatment), and patient education are important.[7,8] Topical calcineurin inhibitors (TCIs) are immunosuppressant agents that are recommended as second-line treatment in areas where skin atrophy is a concern (eg, face, eyelids, skin folds), for steroid-nonresponsive AD, when steroids are not advisable, or when a TCS treatment holiday is necessary.[7,8] Transient localized burning and itching can occur with TCIs, which can limit their use in some patients.[7,8]

Crisaborole ointment is a nonsteroidal, phosphodiesterase 4 (PDE4) inhibitor for the treatment of mild-to-moderate AD.

Multiple clinical trials have evaluated the safety and efficacy of crisaborole in patients with mild-to-moderate AD.[10-14] Crisaborole received its first approval in December 2016 in the United States for the treatment of mild-to-moderate AD in patients aged 2 years and older.

Although results of current head-to-head trials to compare crisaborole to other available topical therapies are not available (ClinicalTrials.gov, NCT03539601), a review of efficacy and safety data can contribute to a better understanding of the potential role of crisaborole in treating mild-to-moderate AD. Herein, the data published between 1997 and 2018 supporting the effectiveness and safety of available topical therapies (TCSs, TCIs, and crisaborole) will be reviewed.

LITERATURE ANALYSIS

Our strategy consisted of searching Medline (via PubMed; Table S1) for blinded, vehicle-controlled trials of topical agents published from January 1, 1997 to April 30, 2018. Identified citations were then selected as shown in Figure S1. In total, 134 publications were identified through the search; publications were hand screened for inclusion. 85 publications were excluded based on the abstract; 21 were excluded based on full text. A total of 28 publications are summarized herein (Table 1).[10,11,15-41] The *P* values represent 2 comparator tests unless otherwise specified.

CONSIDERATIONS FOR COMPARISONS

Variety of Assessment Tools

There is no standardized single assessment tool for measuring the severity of AD and therapy response. A systematic review published in 2003 assessed the heterogeneity of AD severity measures, and it was found that only 27% (23 of 85) of randomized controlled trials (RCTs) used a previously published scoring system.[42] The most commonly used disease severity scales include different aspects of AD.[43] The SCORing of Atopic Dermatitis (SCORAD) assesses representative signs of AD and symptoms of pruritus and sleep loss. The Eczema Area and Severity Index (EASI) assesses lesional extent and intensity for each of 4 body regions, and the Investigator's Static Global Assessment (ISGA) and the Investigator's Global Assessment (IGA) assess overall severity by clinical signs.[43] Heterogeneity of severity assessment instruments was also observed for the trials identified in the current search (Table 1): investigators variously used SCORAD, ISGA/IGA, total severity score (TSS), dermatologic sum score, and days on trial without flare (defined by use of TCS). The variety of instruments used to assess the severity of AD, different interpretation of scores, and lack of precise definitions makes comparison of efficacy between clinical trials challenging. The remitting-relapsing course of AD further complicates the interpretation of RCT results because waning disease severity can be misinterpreted as efficacy, especially in clinical trials with small sample sizes.

Vehicle Effects

"Vehicle effects" are an additional challenge, in that vehicle emollient effects may improve barrier function and reduce TEWL leading to improved outcomes in AD, which are observed frequently in vehicle-controlled RCTs.[10,19,26,44] Vehicle composition, which commonly varies from product to product, can also contribute to local application site AEs such as stinging and erythema.[45] For example, a number of trials included in this analysis report more AEs and treatment-related AEs (TRAEs) in the vehicle arm than in the active treatment arm (Table 1).

EFFICACY OF TOPICAL TREATMENTS

Phosphodiesterase 4 Inhibitors

Three vehicle-controlled trials have been conducted to investigate the efficacy of crisaborole ointment, 2%, including 2 identically designed 4 week phase 3 trials[10] and a 6-week phase 2a proof-of-concept trial.[11] In the phase 3 trials, higher proportions of crisaborole-treated patients than vehicle-treated patients achieved the primary endpoint of ISGA of clear (0) or almost clear with ≥2-grade improvement from baseline at day 29 (Study 1: P=0.038; Study 2: P<0.001) (Table 1, Figure 1).[10] Higher proportions of crisaborole-treated patients also achieved the type 1 error-controlled key secondary endpoint of ISGA clear (0) or almost clear (1) versus vehicle (Study 1: 51.7% vs 40.6%, P=0.005; Study 2: 48.5% vs 29.7%, P<0.001).[10] In a separate analysis of secondary endpoints based on Severity of Pruritus Scale (SPS; 4 point rating scale adapted from the Atopic Dermatitis Severity Index (ADSI) to assess pruritus severity with a 24 hour recall[46]), higher proportions of crisaborole-treated patients achieved improvement in pruritus (SPS score ≤1 with ≥1 point improvement from baseline) compared with vehicle (Study 1: 37% vs 21%, P<0.0001; Study 2: 34% vs 21%, P=0.0006), and that crisaborole-treated patients achieved pruritus improvement earlier than vehicle-treated patients (median days, Study 1: 4.0 vs 9.0, P=0.0008; Study 2: 5.0 vs 9.0, P=0.0042).[47] In the phase 2a intrapatient comparison trial, lesion-specific efficacy was assessed by change from baseline in ADSI score (none [0] to most severe [15]).[11] More patients experienced a greater decrease in ADSI score for the crisaborole-treated lesion than the vehicle-treated lesion at day 28 (primary end point; P=0.017) (Table 1, Figure 1) as well as at each of the other time points assessed (days 14 and 42).[11]

Topical Corticosteroids

In 8 articles summarizing 9 trials, the efficacy of low potency (fluocinolone acetonide in peanut oil, 0.01%; desonide hydrogel, 0.05%),[16,17] lower-medium potency (hydrocortisone butyrate ointment and cream, 0.1%),[18,19] medium potency (betamethasone valerate cream, 0.1%; triamcinolone acetonide cream, 0.05%),[20,21] and very high potency (clobetasol propionate cream and lotion, 0.05%)[22,23]TCSs were assessed. Reiterating the importance of vehicle, 7 of these trials explored various vehicles

FIGURE 1. Effect of Topical Treatments on Severity of Atopic Dermatitis. Treatment success defined as [a]PGA 0 or 1 with ≥2-grade change from baseline at day 29 [b]IGSS 0 or 1 with ≥2-grade change in IGSS from baseline at week 4; [c]ISGA clear (0) or almost clear (1) with ≥2-grade improvement from baseline at day 29; [d]GSS 0, 0.5, or 1 at week 2; [e]IGA 0 or 1 at end of treatment (Bangert: week 3; Breuer: day 29; Leung: week 6; Eichenfield: day 43; Schneider: week 14); [f]IGADA clear or almost clear at week 6; [g]ISGA of clear (0) or almost clear (1) at day 29; [h]>75% improvement from baseline in PGE at day 22; ipercent reduction in TSS at week 2; [j]≥1-grade improvement in IGA at day 7; [k]≥75% in PGE at day 22; [l]IGA mild or less at week 24; [m]greater decrease in ADSI score from baseline at day 28 for active-treated lesion versus vehicle-treated lesion. ADSI, Atopic Dermatitis Severity Index; bid, twice daily; CI, confidence interval; GSS, Global Severity Score; IGA, Investigator's Global Assessment; IGADA, Investigator's Global AD, Assessment; IGSS, Investigator's Global Severity Score; ISGA, Investigator's Static Global Assessment; ND, not determined; PDE4, phosphodiesterase 4; PGA, Physician's Global Assessment; PGE, Physician's Global Evaluation; PGI, Physician Global Improvement; TCI, topical calcineurin inhibitor; TCS topical corticosteroid.

Drug class	Treatment duration	Scale	N (total)	Reference	*P*-value
Includes clear/almost clear and ≥2-grade improvement criteria					
PDE4 (crisaborole)	4 weeks bid	ISGA[a]	759	Paller (2006): Study 1[10]	0.038
PDE4 (crisaborole)	4 weeks bid	ISGA[a]	763	Paller (2016): Study 2[10]	< 0.001
TCS (low potency)	4 weeks bid	IGSS[b]	381	Hebert (2007): Study 1[17]	< 0.001
TCS (low potency)	4 weeks bid	IGSS[b]	201	Hebert (2007): Study 2[17]	< 0.001
TCS (low-medium potency)	1 month bid	PGA[c]	264	Abramovits (2010)[19]	< 0.001
Includes clear/almost clear criterion					
PDE4 (crisaborole)	4 weeks bid	ISGA[d]	759	Paller (2016): Study 1[10]	0.005
PDE4 (crisaborole)	4 weeks bid	ISGA[d]	763	Paller (2016): Study 2[10]	< 0.001
TCS (medium potency)	2 weeks bid	IOAE[f]	629	Larsen (2007)[21]	0.001
TCS (very high potency)	2 weeks bid	GSS[e]	224	Breneman (2005)[23]	0.001
TCI (pimecrolimus)	3 weeks bid	IGA[g]	67	Bangert (2011)[31]	ND
TCI (pimecrolimus)	4 weeks bid	IGA[g]	196	Breuer (2004)[32]	< 0.001
TCI (tacrolimus)	6 weeks bid	IGADA[h]	317	Schachner (2005)[26]	< 0.0001
TCI (pimecrolimus)	6 weeks bid	IGA[g]	53	Leung (2009)[33]	ND
TCI (pimecrolimus)	6 weeks bid	IGA[g]	403	Eichenfield (2002)[34]	≤ 0.005
TCI (pimecrolimus)	14 weeks bid	IGA[g]	1091	Schneider (2016)[40]	0.96
TCI (pimecrolimus)	6 months bid	IGA[g]	250	Kapp (2002)[39]	0.03
Other defintions					
PDE4 (crisaborole)	6 weeks bid	ADSI[l]	25	Murrell (2015)[11]	0.017
TCS (low potency)	2 weeks bid	PGI[j]	94	Paller (2003)[16]	< 0.001
TCI (pimecrolimus)	7 days bid	IGA[k]	198	Kaufmann (2006)[28]	< 0.001
TCI (tacrolimus)	22 days bid	PGE[l]	180	Boguniewicz (1998): 0.03%[25]	0.005
TCI (tacrolimus)	22 days bid	PGE[l]	–	Boguniewicz (1998): 0.1%[25]	0.007
TCI (tacrolimus)	22 days bid	PGE[l]	–	Boguniewicz (1998): 0.3%[25]	0.004
TCI (pimecrolimus)	24 weeks bid	IGA[m]	192	Meurer (2002)[35]	< 0.001

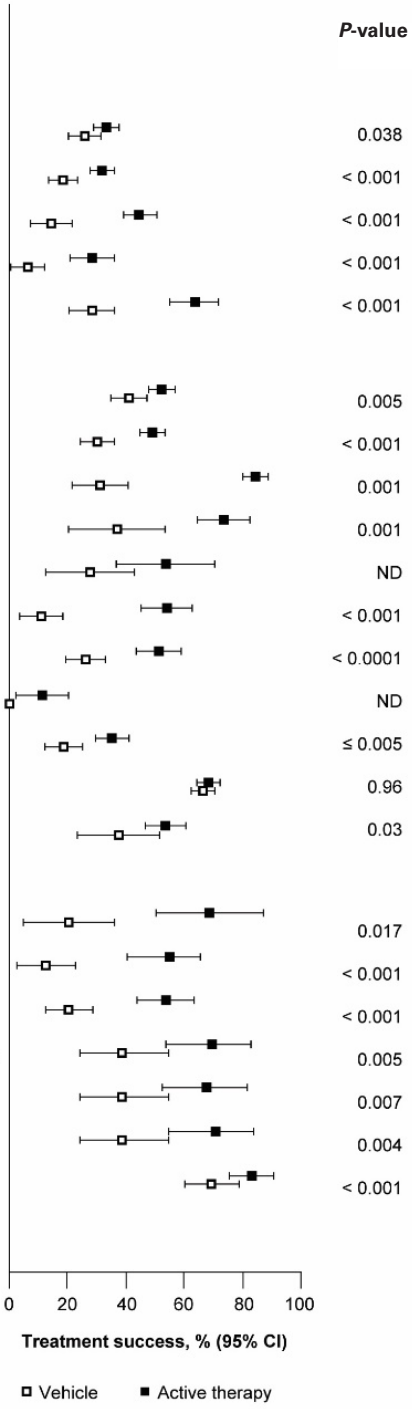

TABLE 1.

Multicenter, Randomized, Blinded, Vehicle-Controlled AD/Eczema Trials of Published January 1997-April 2018						
Reference and Population	**Treatment**	**Primary Efficacy**		**Primary Safety**		
TOPICAL PHOSPHODIESTERASE 4 INHIBITORS						
Paller (2016)[10] - Age ≥2 years - ISGA[c] mild (2) or moderate (3)	4 weeks bid	Proportion of patients with ISGA[c] clear (0) or almost clear (1) with ≥2-grade improvement at day 29		Overall TEAEs, SAEs, TRAEs not reported		
		Study 1	Study 2			
	Crisaborole ointment, 2% (N=507 | N=514)	32.8%, *P*=0.038 vs vehicle	31.4%, *P* <0.001 vs vehicle			
	Vehicle (N=256 | N=250)	25.4%	18.0%			
Murrell (2015)[11] - Age 18-75 years - 2 comparable lesions ~10-500 cm² - ADSI[d] ≥6 to ≤12 with between-lesion difference ≤1	6 weeks bid	Proportion of patients with greater decrease in ADSI[d] versus other lesion at day 28		AEs	SAEs	TRAEs not reported
	(N=25)[b] Crisaborole ointment, 2%	68%, *P*=0.017 vs vehicle		44%	0%	
	Vehicle	20%				
TOPICAL CORTICOSTEROIDS						
Paller (2003)[16] - Age 2-12 years - Moderate-to-severe AD - %BSA ≥20	2 weeks bid	Improvement in symptoms[e] at week 1		Overall AEs not reported	SAEs	Overall TRAEs not reported
	Fluocinolone acetonide in peanut oil, 0.01% (N=49)	Erythema: *P*<0.005 vs vehicle Scaling: *P*<0.005 vs vehicle Lichenification: *P*<0.005 vs vehicle Pruritus: *P*<0.005 vs vehicle			0%	
	Vehicle (N=45)	NR			0%	
Hebert (2007)[17] - Age 3 months-18 years - IGSS[f] mild or moderate	4 weeks bid	Proportion of patients with IGSS[f] clear (0) or almost clear (1) with ≥2-grade change at week 4		AEs	SAEs	TRAEs not reported
		Study 1	Study 2	Pooled	Pooled	
	Desonide hydrogel, 0.05% (N=289 | N=136)	44%, *P*<0.001	28%, *P*<0.001	20%	0.2%	
	Vehicle (N=136 | N=65)	14%	6%	29%	0%	
Gong (2006)[18] - Age 2-65 years - Chinese patients with eczema (N=208) or AD (N=119)	28 days qd	≥50% improvement in symptom and sign scores at day 28		Safety not reported		
	Hydrocortisone butyrate ointment, 0.1% + mupirocin (N=160)	85.0%, NS vs hydrocortisone butyrate + vehicle				
	Hydrocortisone butyrate ointment, 0.1% + vehicle (N=167)	83.2%				
Abramovits (2010)[19] - Age 3 months-<18 years - PGA[g] mild (39%) or moderate (61%)	1 month bid	PGA[g] clear (0) or almost clear (1) with ≥2-grade reduction at day 29		AEs	SAEs	TRAEs
	Hydrocortisone butyrate lipocream, 0.1% (N=131)	63%, *P*<0.001 vs vehicle		21%	0%	2%
	Vehicle (N=133)	28%		22%	0%	2%
Cato (2001)[20] - Age 18-86 years - ≥3 stable or worsening AD lesions for ≥1 year with 2 of 3 having total disease sign and symptom score[h] ≥7	2 weeks bid	Reduction in total disease sign and symptom score[h]		AEs	SAEs	TRAEs not reported
	Triamcinolone acetonide, 0.05%[i]/laurocapram (N=50)	Day 15: *P*=0.01 vs triamcinolone acetonide Day 3: *P*<0.01 vs vehicle		6%	0%	
	Triamcinolone acetonide, 0.05%[i] (N=50)	NR		8%	0%	
	Vehicle (N=50)	NR		20%	0%	
Larsen (2007)[21] - Age ≥6 years - Infected AD - Target lesion ≥4×4 cm²	Betamethasone valerate (1 mg/g)/fusidic acid (20 mg/g), bid for 2 weeks	Percentage reduction in TSS[j] at week 2		AEs		
	Lipid cream (N=275)	82.9%, *P*<0.001 vs vehicle		13.5%	SAEs, TRAEs not reported	
	Cream (N=264)	82.7%		10.5%		
	Lipid cream vehicle (N=90)	33%		21.6%		
Maloney (1998)[22] - Age ≥12 years - Moderate-to-severe AD - %BSA ≥2	4 weeks bid	Mean change in lesion TSS[k]		AEs		TRAEs
	Clobetasol propionate emollient cream, 0.05% (N=41)	Days 4, 8, 15, 29, and 43: *P*<0.001 vs vehicle		2.4%	SAEs not reported	2.4%
	Vehicle (N=40)	NR		5.0%		5.0%
Breneman (2005)[23] - Age 12-86 years - DSS[l] ≥6 in target area + ≥3 signs/symptoms (pruritus, flexural lichenification, linearity in adults, chronic/chronically relapsing dermatitis, history of atopy)	Clobetasol propionate, 0.05%, bid for 2 weeks	Proportion of patients with GSS[m] of 0, 0.5, or 1 at week 2		Overall AEs, SAEs, TRAEs not reported		
	Lotion (N=96)	72.9%, *P*=0.001 vs vehicle, NS vs emollient cream				
	Emollient cream (N=100)	74.0%				
	Vehicle (N=33)	36.4%				
TOPICAL CALCINEURIN INHIBITORS						
Ruzicka (1997)[24] - Age 13-60 years - Moderate-to-severe AD (Rajka and Langeland criteria) - Lesion size ≥200-1000 cm²	3 weeks bid	Median percentage decrease in TSS[n] at week 3		AEs		
		Trunk & extremities	Face & neck			
	Tacrolimus ointment, 0.03% (N=54)	66.7%, *P*<0.001 vs vehicle[o]	71.4%, *P*<0.001 vs vehicle[o]	59.2%	SAEs, TRAEs not reported	
	Tacrolimus ointment, 0.1% (N=54)	83.3%, *P*<0.001 vs vehicle[o]	83.3%, *P*<0.001 vs vehicle[o]	61.1%		
	Tacrolimus ointment, 0.3% (N=51)	75.0%, *P*<0.001 vs vehicle[o]	83.3%, *P*<0.001 vs vehicle[o]	62.7%		
	Vehicle (N=54)	22.5%	25.0%	42.6%		
Boguniewicz (1998)[25] - Age 7-16 years - Moderate-to-severe AD - %BSA=5-30	22 days bid	Proportion of patients with ≥75% improvement in PGE[p] at day 22		Overall AEs, SAEs, TRAEs not reported		
	Tacrolimus ointment, 0.03% (N=43)	69%, *P*=0.005 vs vehicle				
	Tacrolimus ointment, 0.1% (N=49)	67%, *P*=0.007 vs vehicle				
	Tacrolimus ointment, 0.3% (N=44)	70%, *P*=0.004 vs vehicle				
	Vehicle (N=44)	38%				

TABLE 1. (CONTINUED)

Multicenter, Randomized, Blinded, Vehicle-Controlled AD/Eczema Trials of Published January 1997-April 2018						
Reference and Population	**Treatment**	**Primary Efficacy**		**Primary Safety**		
Schachner (2005)[26] - Age 2-15 years - IGADA[q] mild (1) or moderate (2) - Individual assessment score[r] of mild (1) or moderate (2) for ≥3 signs/symptoms of AD (erythema; edema, induration, papulation; excoriations; oozing, weeping, crusting; scaling; lichenification) - %BSA=2-30	6 weeks bid	Proportion of patients with IGADA[q] clear or almost clear at week 6		AEs	SAEs, TRAEs not reported	
	Tacrolimus ointment, 0.03% (N=158)	50.6%, *P*<0.0001 vs vehicle		36.7%		
	Vehicle (N=159)	25.8%		45.3%		
Breneman (2008)[27] - Age ≥2 years - PSGA[s] clear (0) or almost clear (1)	Once daily 3× weekly for 40 weeks	Mean number of flare-free days over 40 weeks		Overall AEs, AEs, TRAEs not reported		
	Tacrolimus ointment, 0.03% (ages 2-15 years), 0.1% (ages ≥16 years) (N=125)	177.4 days, *P*=0.003 vs vehicle				
	Vehicle (N=72)	134.1 days				
Kaufmann (2006)[28] - Age 18-81 years - IGA mild (2) or moderate (3) - %BSA ≥5 - Pruritus score[t] of moderate (2) or severe (3)	7 days bid	Time to ≥1-point improvement in pruritus score[t]	Proportion of patients with ≥1-point improvement in pruritus score[t] at day 2	AEs	SAEs, TRAEs not reported	
	Pimecrolimus cream, 1% (N=100)	2 days, *P*=0.0001 vs vehicle	56%, *P*=0.003 vs vehicle	20.0%		
	Vehicle (N=98)	4 days	34%	17.3%		
Guttman-Yassky (2017)[29] - Age 18-71 years - IGA mild (2) or moderate (3)	2 weeks qd	Percentage reduction in TSS[u] at day 15		AEs	SAEs	TRAEs
	(N=30)[b] Pimecrolimus cream, 1%	39.6%, *P*=0.26 vs vehicle		73.3%	0%	0%
	(N=30)[b] Betamethasone dipropionate cream, 0.05%	66.7%, *P*<0.001 vs vehicle				
	(N=30)[b] Clobetasol propionate, 0.05%[i]	75.5%, *P*<0.001 vs vehicle				
	(N=30)[b] Vehicle	29.8%				
Spergel (2007)[30] - Age 2-65 years - Symmetrical AD lesions on 2 extremities with severe AD (modified EASI[v] >7)	2 weeks	Change in modified EASI[v] at week 2		AEs	SAEs not reported	TRAEs
	(N=45)[b] Pimecrolimus cream, 1% bid + fluticasone propionate cream, 0.05% qd	*P*=0.262 vs vehicle + fluticasone propionate		21.3%		0%
	(N=45)[b] Vehicle bid + fluticasone propionate cream, 0.05% qd	NR				
Bangert (2011)[31] - Age ≥20 years - IGA mild (2) or moderate (3) - Acute episode of mild or moderate AD within 5 days of baseline - Bilateral arm/leg lesions with local EASI=1-8	3 weeks bid to post-lesion skin to prevent relapse (following open-label run-in with TCS for ≤2 weeks to induce remission [local EASI ≤1])	Proportion of patients with IGA clear (0) or almost clear (1) at week 3	Proportion of patients with local EASI <2 for any sign of AD at week 3	Overall AEs, SAEs, TRAEs not reported		
	Pimecrolimus cream, 1% (N=34)	53.0%	73.5%			
	Vehicle (N=33)	27.3%	39.4%			
Breuer (2004)[32] - Age 3-23 months - IGA mild (2) to very severe (5) - %BSA ≥5	4 weeks bid	Percentage change in EASI at day 29		Safety not reported		
	Pimecrolimus cream, 1% (N=130)	-71.5%, *P*<0.001 vs vehicle				
	Vehicle (N=66)	19.4%				
Leung (2009)[33] - Age 2-49 years - IGA mild (2) or moderate (3) - %BSA ≥5 - Documented clinical insensitivity to TCS - Colonization with *S aureus*	6 weeks bid	Mean decrease in EASI at week 3	Percentage change ± SD in EASI at week 6	Overall AEs, SAEs, TRAEs not reported		
	Pimecrolimus cream, 1% (N=47)	*P*=0.043 vs vehicle	1.8% ± 81.3%			
	Vehicle (N=26)	NR	26.9% ± 99.8%			
Eichenfield (2002)[34] - Age 1-17 years - IGA mild (2) or moderate (3) - %BSA ≥5	6 weeks bid (following 7 days of emollient before baseline)	Proportion of patients with IGA clear (0) or almost clear (1) at day 43		Overall AEs, SAEs, TRAEs not reported		
	Pimecrolimus cream, 1% (N=267)	34.8%, *P*≤0.05 vs vehicle				
	Vehicle (N=136)	18.4%				
Meurer (2002)[35] - Age 18-69 years - IGA moderate (3) or severe (4) - %BSA ≥5	24 weeks bid (TCS as needed after 3 days if AD worsened)	Mean percentage (95% CI) of days with TCS use over 24 weeks	Proportion of patients with no TCS use over 24 weeks	AEs, SAEs not reported		TRAEs
	Pimecrolimus cream, 1% (N=96)	14.2% (8.3%, 21.1%), *P*<0.001 vs vehicle	49.0%			24.0%
	Vehicle (N=96)	37.2% (30.4%, 44.0%)	21.9%			20.8%
Zuberbier (2007)[36] - Age 2-17 years - Severe AD (Rajka and Langeland grade 8/9) - Responded to 7-21 days of prednicarbate cream, 0.25%, bid for flare in screening phase	24 weeks bid (prednicarbate reinitiated in case of flare)	Mean percentage ± SD of days with TCS use over 24 weeks		AEs	SAEs not reported	TRAEs
	Pimecrolimus cream, 1% (N=95)	29% ± 25%, *P*=0.1841 vs vehicle		86%		5.3%
	Vehicle (N=89)	35% ± 25%		85%		4.5%

TABLE 1. (CONTINUED)

Multicenter, Randomized, Blinded, Vehicle-Controlled AD/Eczema Trials of Published January 1997-April 2018

Reference and Population	Treatment	Primary Efficacy		Primary Safety		
Sigurgeirsson (2008)[37] – Age 2-17 years – History of IGA of mild (2) or moderate (3), IGA clear (0) or almost clear (1) at baseline	26 weeks bid initiated at signs of recurring AD (TCS as needed after 3 days if AD worsened)	Mean number ± SD of days with no TCS use over 26 weeks		Overall AEs, SAEs not reported		TRAEs
	Pimecrolimus cream, 1% (N=256)	160.2 ± 36.3 days, *P*<0.0001 vs vehicle				9.3%
	Vehicle (N=265)	137.7 ± 51.9 days				10%
Gollnick (2008)[38] – Age ≥18 years – History of IGA mild (2) or moderate (3), IGA clear (0) or almost clear (1) at baseline	26 weeks bid initiated at signs of recurring AD (TCS as needed after 3 days if AD worsened)	Mean number ± SD of days with no TCS use over 26 weeks		Overall AEs not reported	SAEs	TRAEs not reported
	Pimecrolimus cream, 1% (N=277)	152.0 ± 44.0 days, *P*<0.001 vs vehicle			1.9%	
	Vehicle (N=266)	138.7 ± 53.2 days			2.8%	
Kapp (2002)[39] – Age 3-23 months – AD diagnosis (Seymour criteria) – IGA at least mild (≥2) – %BSA ≥5	1 year bid initiated at signs of recurring AD (TCS as needed for flares)	Proportion (95% CI) of patients with no flares		Overall AEs, SAEs, TRAEs not reported		
		Month 6	Month 12			
	Pimecrolimus cream, 1% (N=204)	67.6% (61.2%, 74.1%), *P*<0.001 vs vehicle[w]	56.9 (50.1%, 63.7%), *P*<0.001 vs vehicle[w]			
	Vehicle (N=46)	30.4% (17.1%, 43.7%)	28.3% (15.2%, 41.3%)			
Schneider (2016)[40] – Age 3-18 months – IGA at least mild (≥2) – AD for ≤3 months	3 years bid as needed (TCS as needed after 3 days if AD worsened)	Difference vs vehicle in proportion (95% CI) of patients with no TCS use		AEs	SAEs	TRAEs not reported
		Week 14 (end of investigator-initiated TCS period)	Week 158 (end of double-blind phase)			
	Pimecrolimus cream, 1% (N=546)	–0.088 (–0.123, –0.053), *P*=0.001 vs vehicle	0.005 (–0.029, 0.038), *P*=0.79 vs vehicle	89.5%	7.7%	
	Vehicle (N=545)			87.7%	6.8%	

AD, atopic dermatitis; ADSI, Atopic Dermatitis Severity Index; AE, adverse event; bid, twice daily; BSA, body surface area; CI, confidence interval; DSS, Dermatologic Sum Score; EASI, Eczema Area and Severity Index; GSS, Global Severity Scale; IGA, Investigator's Global Assessment; IGADA, Investigator's Global AD Assessment; IGSS, Investigators Global Severity Score; ISGA, Investigator's Static Global Assessment; NR, not reported; PGE, Physician's Global Evaluation; PGA, Physician's Global Assessment; PSGA, Physician's Static Global Assessment; qd, once daily; SAE, serious AE; SCORAD, SCORing of Atopic Dermatitis; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TRAE, treatment-related AE; TSS, total severity score.

[a]TSS calculated as the sum of severity scores for erythema, edema/papulation, oozing/crusting, excoriations, and lichenification rated from absent (0) to severe (3)
[b]Intrapatient comparison
[c]ISGA ranged from clear (0) to severe (4)
[d]ADSI ranged from none (0) to most severe (15)
[e]Improvement in erythema, scaling, lichenification, and pruritus severity rated from none (0) to very severe (4)
[f]IGSS rated as clear (0) to very severe (5) for Study 1, and clear (0) to severe (4) for Study 2
[g]PGA rated as clear (0) to severe (4)
[h]Total disease sign and symptom score calculated as the sum of severity scores for erythema, induration, and pruritus rated from absent (0) to markedly severe (6)
[i]Formulation not specified
[j]TSS calculated as the sum of severity scores for erythema, edema/papulation, oozing/crusting, and excoriation rated from absent (0) to severe (3)
[k]TSS calculated as the sum of severity scores for erythema, pruritus, induration/papulation, lichenification, erosion/oozing/crusting, and scaling/dryness rated from absent (0) to severe (3)
[l]DSS calculated as the sum of severity scores for erythema, excoriation, and induration/papulation rated from none (0) to severe (4)
[m]GSS ranged from none (0) to severe (4)
[n]TSS calculated as the sum of severity scores for erythema, edema, and pruritus rated from absent (0) to severe (3)
[o]By Jonckheere test
[p]PGE rated as worse (<0% clinical improvement) to cleared (100% clinical improvement)
[q]IGADA rated as clear, almost clear, mild, moderate, severe, or very severe
[r]Individual assessment score rated as absent (0) to severe (3)
[s]PSGA rated from clear (0) to very severe (5)
[t]Pruritus rated from absent (0) to severe (3)
[u]TSS calculated as the sum of severity scores for erythema, edema/papulation, oozing/crusting, excoriation, lichenification, and dryness rated from absent (0) to severe (3)
[v]Modified EASI calculated as the sum of severity scores for erythema, infiltration/papulation, excoriation, and lichenification rated from mild (0) to severe (3)
[w]By Van Elteren test

for established TCS designed to expand indications,[16] eliminate alcohol and surfactants,[17] improve penetration,[20] ease dryness,[21] and provide additional formulation options.[23]

Of these, 8 trials showed significant improvement in AD severity or symptoms in patients who received TCS compared with vehicle by end of treatment (Table 1, Figure 1). In one of the earliest trials captured within the limits of this search, lesion TSS was significantly improved by day 4 for clobetasol propionate compared with vehicle ($P \leq 0.006$), and remained significantly improved through end of treatment (day 43; $P<0.001$) (Table 1).[22] In a phase 3 trial investigating the efficacy and safety of hydrocortisone butyrate cream, 0.1%, more hydrocortisone butyrate-treated patients exhibited Physician's Global Assessment (PGA) success at day 29 (primary endpoint; PGA clear (0) or almost clear (1) with ≥2-grade reduction) compared with vehicle-treated patients ($P<0.001$) (Table 1, Figure 1).[19]

One trial explored the benefit of adding the antibiotic mupirocin to hydrocortisone butyrate cream, 0.1%.[18] There was no difference in the primary efficacy endpoint (percentage improvement in signs and symptoms) between patients who received hydrocortisone butyrate + mupirocin and those who received hydrocortisone butyrate + vehicle at the end of treatment (day 28) (Table 1); however, differences were observed earlier in treatment (day 7).[18]

Topical Calcineurin Inhibitors

Tacrolimus

Four tacrolimus ointment publications fit the criteria for this analysis. Significant differences compared with vehicle were reported for the primary endpoint in each (Table 1).[24-27]

In a phase 2 trial of tacrolimus in patients aged 13-60 years, median decreases in TSS (erythema, edema, and pruritus) at week 3 (primary endpoint) were significantly different between each dosage of tacrolimus and vehicle ($P<0.001$ via Jonckheere test) (Table 1), with no differences among tacrolimus dosages.[24] The efficacy of tacrolimus ointment was further explored in children.[25] The primary efficacy endpoint, physician global evaluation (PGE) of clinical response on a scale of worse (<0%) to cleared (100%), was significantly improved for each dosage of tacrolimus compared with vehicle at the end of treatment (day 22; Table 1, Figure 1).[25]

Additional efficacy endpoints were explored in the remaining 2 tacrolimus trials. In the first trial, significantly more tacrolimus-treated than vehicle-treated patients achieved the primary efficacy endpoint of Investigator's Global AD Assessment (IGADA) clear or almost clear at week 6 ($P<0.0001$; Table 1; Figure 1).[26] In the second trial, the mean number of flare-free treatment days and the time to first relapse were significantly longer in patients who received tacrolimus compared with vehicle ($P=0.003$ and 0.037, respectively) (Table 1).[27]

Pimecrolimus

Multiple studies have substantiated the efficacy of pimecrolimus cream based on primary efficacy endpoints of improvement in pruritus,[28] decrease in EASI or local EASI,[31-33] proportion of patients achieving IGA clear (0) or almost clear (1),[31,34] reduction in the need for TCS,[35,37,38] and proportion of patients who remained flare free.[39] However, in other studies, significant differences were not reported for the primary efficacy endpoint (Table 1).[29,30,36,40]

In comparison with vehicle in trials of 3-4 weeks in duration, pimecrolimus treatment resulted in significantly more patients achieving IGA clear (0) or almost clear (1) (Table 1, Figure 1)[31,32] and local EASI <2 for any lesion (Table 1)[31] as well as greater changes in IGA score (secondary endpoint; $P<0.001$) (Figure 1)[32] and EASI score ($P<0.001$) (Table 1).[32] In identically designed, 6-week trials, 34.8% of pimecrolimus-treated patients achieved IGA clear (0) or almost clear (1) at day 43 (primary endpoint) compared with 18.4% of those treated with vehicle ($P \leq 0.05$) (Table 1, Figure 1).[34]

Another trial assessed the percentage of days that TCS was used. The primary endpoint was the percentage of days with TCS use.[35] Secondary endpoints included the number of flares, time-to-first flare, proportion of patients with IGA mild or less (≤2) (Figure 1), and changes in EASI score and pruritus severity. By week 24, pimecrolimus-treated patients had significantly fewer days with TCS use than vehicle-treated patients ($P<0.001$) and a higher proportion of pimecrolimus-treated than vehicle-treated patients had no TCS use (Table 1).[35] Decrease in TCS use was also seen in several subsequent trials,[37,38] including in patients with mild-to-moderate AD[38,48] and pediatric patients.[37] However, 1 study in patients with severe AD did not show a significant decrease in the mean percentage of days with TCS use for pimecrolimus compared with vehicle (Table 1).[36] Unlike the other "TCS reduction" studies, this study had a screening phase in which all patients applied prednicarbate cream, 0.25%, twice daily for 7-21 days until flare was under control before enrollment in the double-blind portion of the study. After the study, it was determined that, although study centers enrolled patients with high severity scores according to Rajka and Langeland criteria, some patients did not have active disease, as shown by baseline IGA scores of almost clear (1) and mild (2)). When these patients were excluded in a post hoc analysis, there were significantly fewer days with TCS use in patients who received pimecrolimus than in those who received vehicle.[36]

In a 1-year study, significantly more pimecrolimus-treated versus vehicle-treated infants aged 3-23 months remained flare-free through month 6 (primary endpoint; $P<0.001$ Van Elteren test) and month 12 (Table 1), translating into longer flare-free

periods (P<0.001 via log-rank test), fewer flares per year (1.0 vs 2.2, P<0.001 via Van Elteren test), and greater proportions of patients with no TCS use (63.7% vs 34.8%).[39] This reduction in risk of flare was observed regardless of baseline disease severity, including for patients with severe AD.[39] Likewise, the proportion of patients achieving IGA clear (0) or almost clear (1) was significantly greater for pimecrolimus versus vehicle at day 8 (44.6% vs 8.7%; P<0.001) and continuing through month 6 (52.9% vs 37.0%, P<0.03); at month 12, differences remained numerically, but not statistically, greater (53.9% vs 47.8%, P>0.05).[39] Differences in EASI score and proportion of patients achieving pruritus score of none (0) or mild (1) were also significantly greater for pimecrolimus versus vehicle at day 43 and beyond.[39]

The Study of the Atopic March (SAM) was a long-term study of pimecrolimus compared with vehicle in patients aged 3-18 months with IGA ≥2 newly diagnosed with AD.[40] The trial was designed as a 3-year double-blind, dose-escalation study followed by 3 years of open-label pimecrolimus. Coprimary endpoints included proportion of disease-free days (ie, with no TCS use) and longest duration of remission. The study was prematurely halted after a mean follow-up of 2.8 years after the double-blind phase at the recommendation of the independent study monitoring committee based on protocol-specified criteria.[40] TCS could be used for flares; during the first 14 weeks, its use was governed by the investigator, whereas after 14 weeks, TCS could be initiated at the discretion of the caregiver. There was a significant difference between pimecrolimus and vehicle groups in the proportion days with no TCS use at week 14 (P<0.001), but this difference decreased in subsequent weeks and there was no difference at the end of the double-blind phase (week 158) (Table 1).[40] Similar trends were observed for the secondary endpoint of proportion of patients achieving IGA clear (0) or almost clear (1) (Figure 1).[40] It was concluded that, although the SAM trial replicated the short-term efficacy previously observed with pimecrolimus compared with vehicle, the high discontinuation rate (48%) and empowerment of caregivers to initiate rescue TCS could have impacted the ability to identify the efficacy of pimecrolimus long-term.[40]

A randomized, double-blind, parallel-group trial was conducted to investigate the efficacy of pimecrolimus in patients with TCS-insensitive AD, defined as a <35% reduction in EASI after at least 12 days treatment with twice-daily prednicarbate cream, 0.25% (Table 1).[33] The difference in the primary endpoint (decrease in EASI score) between the pimecrolimus and vehicle arms was only significant at week 3 (P=0.043) (Table 1), with large standard deviations and substantial differences between mean and median values, indicating that there was significant variability in patient response.[33] Treatment success, defined as IGA clear (0) or almost clear (1), was achieved by 11% of pimecrolimus-treated patients and zero vehicle-treated patients (Figure 1).[33] Change in lesion-specific IGA scores, pruritus scores, and patient assessment of AD were comparable between the pimecrolimus and vehicle arms.[33]

To evaluate whether TCI plus TCS has a synergistic effect, an exploratory randomized, vehicle-controlled intrapatient comparison trial was conducted to evaluate the efficacy of pimecrolimus twice daily + fluticasone propionate cream, 0.05%, once daily compared with vehicle twice daily + fluticasone propionate cream, 0.05%, once daily in patients with severe AD.[30] Secondary efficacy endpoints included IGA score (Figure 1), local IGA score, and patient/caregiver assessment of eczema severity. At end of treatment, there was no statistically significant difference in change from baseline in modified EASI score at week 2 (primary endpoint, P=0.262) (Table 1).[30] There were also no differences in secondary efficacy endpoints—proportion of patients achieving global or local IGA clear (0) or almost clear (1).[30] Post hoc analyses to explore variables such as age, study site, sex, baseline EASI score, right versus left side, or lesion site found no differences that could predict response.[30]

SAFETY OF TOPICAL TREATMENTS

Phosphodiesterase 4 Inhibitors

In the phase 3 crisaborole trials, the most frequently reported TRAE was application site pain (burning or stinging), which was reported for 4.4% of crisaborole-treated patients and 1.2% of vehicle-treated patients (Table 2); most patients (77.6%) experienced resolution within 1 day of onset.[10] No treatment-related serious AEs (SAEs) were reported. In the long-term (48 weeks), open-label safety extension trial (N=517), no new safety signals were identified, and no evidence of skin atrophy or telangiectasia were reported.[49]

In the phase 2a intrapatient comparison crisaborole trial, AEs were reported for 44% of patients, and TRAEs were reported for 12% of patients (Table 1).[11] These TRAEs included application site events such as erythema, irritation, pain, and pruritus (Table 2).[11] There was no evidence of severe AEs or SAEs.[11]

Topical Corticosteroids

The occurrence of local AEs with TCS is well known, but the true incidence is poorly characterized because of the lack of clinical trials performed to modern standards and because many trials do not report the incidence of TEAEs.[7,8,50] Systemic absorption of TCS also has the potential to lead to systemic AEs, such as hypothalamic-pituitary-adrenal axis suppression[7] and decreased serum cortisol (Table 2). To reduce the risk for systemic absorption of TCS, treatment guidelines include cautions for use with occlusive wrappings, coverage of a high percentage of the body, and prolonged use, especially in small children and infants and on sensitive skin areas (eg, facial skin).[7,8] Additional concerns include TCS addiction and steroid withdrawal syndrome, which are most often associated with

TABLE 2.

Adverse Events of Interest				
Reference	**AEs of interest, n (%)**			
TOPICAL PHOSPHODIESTERASE 4 INHIBITORS				
		Crisaborole ointment, 2% (N=1012)		Vehicle (N=499)
Paller (2016)[10]	Application site pain	45 (4.4)		6 (1.2)
	Application site pruritus	5 (0.5)		6 (1.2)
		Crisaborole ointment, 2% (N=25)		Vehicle (N=25)
Murrell (2015)[11]	Itch and redness	1 (4)		1 (4)
	Contact dermatitis, irritant	1 (4)		NR
	Contact dermatitis, allergic	NR		1 (4)
	Application site stinging	0		1 (4)
TOPICAL CORTICOSTEROIDS				
		Fluocinolone acetonide in peanut oil, 0.01% (N=49)		Vehicle (N=45)
	Hypopigmentation	2 (4.1)		0
Paller (2003)[16]	Rash	1 (2.0)		1 (2.2)
	Telangiectasia	0		0
	Skin atrophy	0		0
		Desonide hydrogel, 0.05% (N=425)		Vehicle (N=157)
	Application site burning	NR (1)		NR
	Rash	NR (1)		NR
Hebert (2007)[17]	Discontinuation because of telangiectasia	1 (<1)		1 (<1)
	Application site pruritus	NR (<1)		0
	Skin atrophy	0		1 (<1)
	Discontinuation because of burning and stinging	0		1 (<1)
		Hydrocortisone butyrate lipocream, 0.1% (N=131)		Vehicle (N=133)
	Dermatitis	0		2 (2)
Abramovits (2010)[19]	Telangiectasia	0		2 (2)
	Erythema	0		1 (1)
	Urticaria	0		1 (1)
Cato (2001)[20]		Triamcinolone acetonide, 0.05%[a]/ laurocapram (N=50)	Triamcinolone acetonide, 0.05%[a] (N=50)	Vehicle (N=50)
	Burning/pruritus/disease exacerbation	3 (6)	2 (4)	6 (12)
		Betamethasone valerate (1 mg/g)/fusidic acid (20 mg/g)		Vehicle (N=88)
		Lipid cream (N=274)	Cream (N=258)	
Larsen (2007)[21]	Any lesional or perilesional AE	7 (2.6)	4 (1.6)	12 (13.6)
	Pruritus	2 (<1)	0	6 (6.8)
	Skin burning	3 (1.1)	3 (1.2)	4 (4.5)
		Clobetasol propionate emollient, 0.05% (N=41)		Vehicle (N=40)
	Pruritus/burning/stinging	1 (2.4)		0
Maloney (1998)[22]	Skin atrophy/pruritus	0		2 (5.0)
	≥50% decrease in serum cortisol	NR (15)		NR (11)
	Serum cortisol below normal range	3 (8)		0
		Clobetasol propionate, 0.05%		Vehicle (N=33)
		Lotion (N=96)	Emollient cream (N=100)	
Breneman (2005)[23]	Clinically significant skin atrophy	0	0	0
	Telangiectasia	0	0	0

TABLE 2. (CONTINUED)

Adverse Events of Interest					
Reference	**AEs of interest, n (%)**				
TOPICAL CALCINEURIN INHIBITORS					
		Tacrolimus ointment			Vehicle (N=54)
		0.03% (N=54)	0.1% (N=54)	0.3% (N=51)	
Ruzicka (1997)[24]	Application site burning	20 (37.0)	25 (46.3)	25 (49.0)	8 (14.8)
	Application site pruritus	7 (13.0)	2 (3.7)	7 (13.7)	4 (7.4)
	Application site erythema	3 (5.6)	6 (11.1)	6 (11.8)	3 (5.6)
	Exacerbation of AD	4 (7.4)	4 (7.4)	2 (3.9)	7 (13.0)
	Discontinuation because of application site AE	1 (1.9)	4 (7.4)	3 (5.9)	2 (3.7)
		Tacrolimus ointment			Vehicle (N=44)
		0.03% (N=43)	0.1% (N=49)	0.3% (N=44)	
Boguniewicz (1998)[25]	Application site pruritus	11 (25.6)	10 (20.4)	13 (29.5)	7 (15.9)
	Application site burning	9 (20.9)	5 (10.2)	10 (22.7)	3 (6.8)
	Application site erythema	0	1 (2.0)	3 (6.8)	2 (4.5)
	Increased serum creatinine	1 (2.3)	0	0	0
		Tacrolimus ointment, 0.03% (N=158)			Vehicle (N=159)
Schachner (2005)[26]	Itching	37 (23.4)			53 (33.3)
	Erythema	12 (7.6)			30 (18.9)
	Burning/stinging	30 (19.0)			27 (17)
	Discontinuation because of application site AE	4 (2.5)			12 (7.5)
	Eczema herpeticum	0			1 (<1)
		Tacrolimus ointment, 0.03% (N=125)			Vehicle (N=71)
Breneman (2008)[27]	Application site burning	2 (1.6)			1 (1.4)
	Increased irritation NOS	2 (1.6)			0
	Application site pruritus	1 (0.8)			2 (2.8)
	Skin infection, other NOS	1 (0.8)			0
	Application site reaction NOS	1 (0.8)			0
	Skin infection, folliculitis	0			0
	Skin infection, molluscum	0			1 (1.4)
		Pimecrolimus cream, 1% (N=100)			Vehicle (N=98)
Kaufmann (2006)[28]	Burning sensation	3 (3.0)			1 (1.0)
	Discontinuation because of application site burning	0			1 (1.0)
	Atopic dermatitis	0			2 (2.0)
	Eczema	0			2 (2.0)
		Pimecrolimus cream, 1% (N=30)	Betamethasone dipropionate cream, 0.05% (N=30)	Clobetasol propionate, 0.05%[a] (N=30)	Vehicle (N=30)
Guttman-Yassky (2017)[29]	Application site reaction	0	1 (4.6)	0	0
Spergel (2007)[30]	Specific application site AEs not reported				
		Pimecrolimus cream, 1% (N=34)			Vehicle (N=33)
Bangert (2011)[31]	Application site reaction	0			1 (3)
		Pimecrolimus cream, 1% (N=47)			Vehicle (N=26)
Leung (2009)[33]	Skin infection	8 (17.0)			2 (7.7)
	Herpes simplex	2 (4.3)			0
		Pimecrolimus cream, 1% (N=267)			Vehicle (N=136)
Eichenfield (2002)[34]	Any local AE	NR (28)			NR (35)
	Application site burning	NR (10.4)			NR (12.5)

TABLE 2. (CONTINUED)

Adverse Events of Interest			
Reference	**AEs of interest, n (%)**		
Meurer (2002)[35]		Pimecrolimus cream, 1% (N=96)	Vehicle (N=96)
	Local AEs	38 (39.6)	35 (36.5)
	Any skin infection	18 (18.8)	9 (9.4)
	Herpes	10 (10.4)	5 (5.2)
	Bacterial	4 (4.2)	3 (3.1)
	Fungal	2 (2.1)	1 (1.0)
	Application site burning	10 (10.4)	3 (3.1)
	Eczema herpeticum	0	2 (2.1)
Zuberbier (2007)[36]		Pimecrolimus cream, 1% (N=95)	Vehicle (N=89)
	Treatment-related		
	Application site burning	2 (2.1)	1 (1.1)
	Herpes simplex	1 (1.1)	NR
	Impetigo	1 (1.1)	1 (1.1)
	Molluscum contagiosum	1 (1.1)	NR
	Keratitis	NR	1 (1.1)
	Blepharitis	NR	1 (1.1)
	Conjunctivitis	NR	1 (1.1)
	Herpes virus infection	NR	1 (1.1)
	Contact dermatitis	NR	1 (1.1)
Sigurgeirsson (2008)[37]		Pimecrolimus cream, 1% (N=246)	Vehicle (N=260)
	Impetigo	9 (3.7)	6 (2.3)
	Varicella	9 (3.7)	8 (3.1)
	Urticaria	8 (3.3)	4 (1.5)
	Molluscum contagiosum	6 (2.4)	8 (3.1)
	Application site burning	3 (1.2)	8 (3.1)
	Eczema herpeticum	1 (<1)	0
Gollnick (2008)[38]		Pimecrolimus cream, 1% (N=264)	Vehicle (N=254)
	Application site burning	11 (4.2)	2 (<1)
	Herpes simplex virus infection	9 (3.4)	12 (4.7)
	Eczema herpeticum	0	1 (<1)
Kapp (2002)[39]		Pimecrolimus cream, 1% (N=204)	Vehicle (N=46)
	Application site reaction	NR (6.5)	NR (14.7)
	Any skin infection	NR (27.0)	NR (27.6)
	Bacterial	NR (12.7)	NR (9.1)
	Viral	NR (3.3)	NR (6.9)
Schneider (2016)[40]	Application site AEs not reported		

AD, atopic dermatitis; AE, adverse event; NOS, not otherwise specified; NR, not reported; SAE, serious AE; TRAE, treatment-related AE.
[a]Formulation not specified.

medium- to high-potency TCSs.[51] Addiction occurs with TCS misuse, resulting in physical or psychological dependence.[52] The most common sign of steroid withdrawal is erythema; other symptoms include burning/stinging, pain, pruritus, facial hot flashes, and exacerbation with heat or sun.[51] The recurrence of AD symptoms and/or the signs of steroid withdrawal when TCS use is stopped often leads patients to restart TCS.[52] As a consequence of the safety concerns associated with TCS treatment and steroid withdrawal syndrome, many patients develop steroid phobia, which can hinder adherence and can result in undertreatment.[53-55]

The lack of consistent reporting of AEs makes it difficult to compare AEs among TCSs (Tables 1 and 2). Common local adverse reactions reported by those who received TCS in the trials summarized herein included secondary infections, eczema herpeticum, contact dermatitis, burning, itching, and skin atrophy ranging in incidence from 0% to 12% (Table 2).[16,17,19-23] Skin atrophy and telangiectasia were reported in few trials; incidence was low when reported (maximum reported: <1% for skin atrophy and 2% for telangiectasia) (Table 2).[16,17,19,23]

Few studies evaluated systemic AEs, likely as a result of the short duration of the trials (2-4 weeks), reflecting current treatment guidelines.[7,8] One study evaluated the effect of TCS on serum cortisol.[22] In the clobetasol propionate group, 15% of patients experienced ≥50% decrease in serum cortisol level, compared with 11% in the vehicle group (P=0.737) (Table 2).[22] In addition, 3 patients (8%) in the clobetasol propionate arm experienced serum cortisol below the normal range compared with 0 patients in the vehicle arm (P=0.240) (Table 2).[22]

Topical Calcineurin Inhibitors

The addition of TCIs to the treatment paradigm in the early 2000s provided an alternative for situations in which the safety of TCSs was of concern, such as in patients with steroid-induced atrophy, for those who required long-term uninterrupted topical anti-inflammatory treatment, and for the treatment of sensitive skin areas.[7] The most frequently reported local TEAEs associated with TCIs include application site burning or pruritus, which typically improve as lesions resolve.[7] The more significant concern with TCIs is the possibility that their use is associated with immune system-mediated malignancy. In 2006, the US Food and Drug Administration required that a boxed warning regarding the theoretical risk for malignancy be included in TCI prescribing information in response to widespread off-label use in children <2 years of age.[7,56,57] Even though no causative link between TCI use and malignancy has been established,[57-60] the boxed warning remains.

Unlike in the TCS studies, extensive safety data were reported in the TCI trials identified in this search. Tacrolimus was well tolerated when applied once or twice daily at least 3 times weekly for up to 40 weeks in those aged ≥2 years,[24-27] and pimecrolimus was well tolerated in those aged ≥2 years for up to 26 weeks[28-31,33-38] and in those aged <2 years for up to 3 years[39,40] (and up to 5 years in an open-label study,[61] which is outside the scope of this review) (Tables 1 and 2). Application site AEs were most frequently reported for tacrolimus (although causality was not often reported), and incidence ranged from 1.4% to 49% for burning, 0.8% to 29.5% for pruritus, and 0% to 11.8% for erythema (Table 2).[24-27] Among those who received pimecrolimus, application site burning was reported by 1.2% to 10.4% of patients; application site pruritus and erythema were less likely to be reported (Table 2).

CONCLUSIONS

Topical drugs to treat AD include PDE4 inhibitors, TCSs, and TCIs. In the absence of head-to-head trials, comparison among available agents is difficult because of the different study designs, endpoints, and methodologies used across published clinical studies. A lack of precise outcome definitions and consistent safety reporting further complicate comparison among trials. For example, in the current literature analysis, 12 of 28 publications did not report total AEs (Table 1), and individual AE reporting and causality assessments varied. This is in part because of changes in guidelines for reporting of clinical trial results over the duration of the literature search, including the adoption of guidelines such as the CONSORT statement[62] and the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals adopted by the International Committee of Medical Journal Editors.[63] The topical PDE4 inhibitor crisaborole represents a novel therapy targeting proinflammatory factors involved in AD pathogenesis. The completed clinical studies for crisaborole demonstrate efficacy and a favorable safety profile, enabling health care providers to include crisaborole among topical therapeutic options available for the treatment of mild-to-moderate AD.

DISCLOSURES

Lawrence Eichenfield has been a consultant, investigator, data safety monitoring board member, or speaker for Pfizer Inc., Allergan, Anacor, Arcutis, Dermavant, Dermira, Eli Lilly, Galderma, LEO Pharma, Medimetriks, Novartis, Otsuka, Regeneron, Sanofi-Genzyme, OrthoDerm/Valeant, and UCB.

Thomas Luger has no conflicts of interest to disclose.

Kim Papp has been a consultant, scientific adviser, investigator, scientific officer, and/or speaker for Pfizer Inc., AbbVie, Akros, Allergan, Amgen, Anacor, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter, Bausch Health, Boehringer Ingelheim, BMS, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Hakka Kirin, LEO Pharma, Medimmune, Meiji Seika Pharma, Merck Sharp & Dahme, Merck-Serano, Mitsubishi

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Debra Sierka, Anna Tallman, and William Ports were employees and stockholders of Pfizer Inc., at the time of this work.

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