Tolerability of Topical Treatments for Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a common inflammatory skin disease that is accompanied by increased sensitivity to itch-provoking and pain-provoking stimuli. Patients with AD experience skin pain before initiation of therapy and have also reported painful application site reactions in clinical trials of emollients and prescription topical therapies, including topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), and a topical phosphodiesterase 4 (PDE4) inhibitor. To compare the sensory tolerability of prescription topical therapies for AD, a comprehensive literature search and analysis of published clinical trials was conducted. Sensory tolerability issues such as application site pain, burning, stinging, and pruritus were often among the most common adverse events or treatment-related adverse events in clinical trials for prescription topical therapies. Tolerability issues occurred at highest rates in trials of TCIs, followed by trials of the PDE4 inhibitor crisaborole and TCSs, although direct comparisons are not possible because of differences in study design. Tolerability issues in these clinical trials were generally mild to moderate and transient. This article also reviews published strategies for managing sensory tolerability issues in AD patients during treatment with topical therapies.

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Keywords: Atopic dermatitis; Application site pain; Application site reaction; Calcineurin inhibitor; Corticosteroid; Crisaborole; Tolerability; Topical therapy

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous
lesions and pruritus that affects up to 15–30% of children and 2–10% of adults [1, 2]. In one study, the prevalence of baseline skin pain in AD was 42.7%, with 13.8% of patients experiencing severe or very severe pain [3], although some studies estimate pain prevalence rates exceeding 50% [4] and 80% [5]. High prevalence of pain may relate to skin sensitivity. Patients with AD are more likely than healthy individuals to report hypersensitivity to lactic acid [6], nonhistaminergic chemical stimuli [7], and pain- and itch-provoking mechanical stimuli [7]. Proposed mechanisms of skin sensitivity and pain in AD include epidermal barrier disruption, leading to increased exposure of cutaneous nerve endings and heightened vulnerability to environmental irritants; increased density or length of cutaneous nerve fibers; and inflammation-mediated sensitization of afferent neurons containing receptors for pain, itch, and warmth such as transient receptor potential cation channel subfamily V member 1 (TRPV1) [3, 7–9]. Scratching is also a likely source of pain because pain prevalence is significantly associated with having skin excoriations [3].

Topical therapies are the cornerstone of AD management, beginning with emollients and moisturizers as first-line therapies [10–12]. Topical corticosteroids (TCSs), which suppress antigen processing and proinflammatory cytokine release in immune cells, are first-line anti-inflammatory therapies [10–12]. Second-line therapies include topical calcineurin inhibitors (TCIs), which inhibit calcineurin-dependent activation of T cells [10]. TCIs are recommended for AD unresponsive to TCSs, for situations in which TCS use is inadvisable, and for proactive maintenance (application 2–3 times weekly to flare-prone areas) [10–12]. Crisaborole is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate AD [13]. Crisaborole is recommended by the American College of Allergy, Asthma, and Immunology AD Yardstick, a tool that is intended to supplement published guidelines with the most recent clinical and research findings, for second-line therapy, for patients intolerant of TCSs or TCIs, and for maintenance [14].

Application of topical treatments can exacerbate baseline pain and produce other skin sensory adverse events (AEs) in AD. Tolerability events including skin burning, stinging, and pruritus have been reported with certain emollient formulations [15–18]. TCIs are commonly associated with application site (AS) burning and stinging [10–12], and AS burning and pruritus have been reported for TCSs [19, 20]. AS pain has been reported in clinical trials of crisaborole [21, 22]. The objective of this review is to synthesize published data on the sensory tolerability of topical prescription products for AD and to provide clinical recommendations on mitigation strategies for tolerability issues. We define sensory tolerability issues as burning, stinging, pain, irritation, pruritus, or paresthesia.

LITERATURE ANALYSIS

To compare the sensory tolerability of currently available, prescription topical treatments for AD, we performed a literature analysis (see Fig. 1). Treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs), and discontinuations relevant to tolerability are summarized in Tables 1, 2, 3 and 4. AS-specific data were included whenever available.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

TOLERABILITY OF TCIs

Most studies meeting inclusion criteria evaluated TCIs (Table 1). Among 19 studies assessing pimecrolimus cream, 1% (not compared with tacrolimus), six evaluated short-term treatment (6–12 weeks) [23–28]. All six studies were vehicle controlled for at least part of the study and, with the exception of one study [23] evaluating pimecrolimus combination therapy with TCSs in severe AD, they enrolled patients with mild to moderate AD and did not allow TCSs as concomitant therapy. Prevalence rates of burning/pain/irritation ranged from 1.6% to
26.7% (pimecrolimus) and 1.0% to 22.2% (vehicle). Five of the short-term studies cited burning and/or irritation among the most common TEAEs [24–27] or cutaneous AEs [28]. Thirteen pimecrolimus studies evaluated long-term (approximately 5 months to 1 year) therapy, of which six were controlled, double-blind studies [29–34], four were open-label [35–38], and three had both double-blind and open-label phases [39–41]. Eleven long-term studies allowed occasional treatment with TCSs as rescue therapy for flares [29–38, 40]. Among long-term studies providing overall event-specific rates, rates of AS burning ranged from 0.8% to 10.5% (pimecrolimus) and 1.1% to 9.3% (vehicle/conventional therapy). Seven studies cited tolerability-related AS issues (burning, stinging, pruritus, pain) among the most common AEs [31–33, 35–38]. Eleven pimecrolimus studies (two short-term and nine long-term) provided information on the severity and timing of AS tolerability issues, describing them as predominantly mild to moderate, transient, and/or occurring early in treatment [24, 28, 31–39].

Fifteen studies evaluated tacrolimus ointment, 0.03% or 0.1% (not compared with pimecrolimus). Five studies assessed short-term treatment (4–12 weeks), two of which were vehicle controlled [42–46]. Among three short-term studies providing overall rates or for which overall rates could be calculated, rates of skin burning and pruritus ranged from 19.0% to 52.9% and 16.4% to 33.8%, respectively, in tacrolimus-treated patients versus rates of 17.0% and 33.3% in vehicle-treated patients. Kang et al. [42] reported significantly higher rates of AS burning in groups receiving 12 weeks of treatment with tacrolimus 0.03% or 0.1% than in the vehicle group for head/neck \((p < 0.01)\) and non-head/neck \((p < 0.001)\) areas, and higher prevalence of AS pruritus in the tacrolimus groups than in the vehicle group for non-head/neck areas \((p < 0.05)\). One other short-term study [43] included both 0.03% and 0.1% groups, reporting a numerically higher rate of AS burning in adults treated with 0.1% tacrolimus (69.0%) than in children treated with 0.03% tacrolimus (26.9%), potentially because of the higher strength of tacrolimus used by adults. Schachner et al. [44] reported similar rates of AS burning/stinging in vehicle-treated (17.0%) and tacrolimus-treated (19.0%) children with mild to moderate AD. However, burning/stinging with tacrolimus application
| References | Study design | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus | Frequency of application site paresthesia, other |
|------------|--------------|--------------------------|------------------------|---------------------------------------------------------------|---------------------------------|-----------------------------------------------|
| Reitamo et al. [48] | Phase 3, OL, multicenter, noncomparative study | Mod-sev AD (Rajka and Langeland criteria; 5–60% total BSA), 18–70 years, N = 316 | TAC, 0.1% BID for 6 or 12 months | Burning—43.7% (n = 138) | Pruritus—19.0% (n = 60) | |
| Wahn et al. [32] | DB, randomized controlled study | AD (IGA score ≥ 2; ≥ 5% total BSA), 2–17 years, N = 713 | 2:1 PIM, 1% vs. VEH BID prn for 1 year; TCS for flares; emollients part of both regimens | Burning—10.5% (PIM), 9.3% (VEH) | | |
| Eichenfield et al. [24] | Two randomized, multicenter, DB, vehicle-controlled studies | Mi-mod AD (IGA score of 2 or 3; ≥ 5% total BSA), 1–17 years, N = 403 | 2:1 PIM, 1% vs. VEH BID for 6 weeks | Burning—10.4% (PIM), 12.5% (VEH) | | Local AE—28% (PIM), 35% (VEH) |
| Meurer et al. [34] | Randomized, DB, parallel-group, multicenter study | Mod-sev AD (IGA score of 3 or 4; ≥ 5% total BSA), 18–69 years, N = 192 | 1:1 PIM, 1% vs. VEH BID as needed for 24 weeks; TCS for flares; emollients part of both regimens | Burning—10.4% (n = 10, PIM), 3.1% (n = 3, VEH) | | Discontinuation due to burning—1.0% (n = 1, VEH) |
| Ho et al. [41] | DB, randomized study; followed by 20-week OL safety extension study | Mi-mod AD (IGA score of 2 or 3; ≥ 5% total BSA), 3–23 months, N = 186 | PIM, 1% or VEH BID for 6 weeks (DB); PIM, 1% for 20 weeks (OL) | Irritation—0% (PIM, DB), 4.8% (VEH, DB) | | ASR not otherwise specified—1.6% (PIM, DB), 1.6% (VEH, DB) |
| References | Study design | Patient characteristics | Treatment and duration | Frequency of application site | Frequency of application site | Frequency of application site |
|------------|-------------|-------------------------|------------------------|-----------------------------|-------------------------------|-----------------------------|
| Kang et al. [42] | Three DB, randomized, vehicle-controlled, multicenter studies | Mod-sev AD (Rajka and Langeland criteria), 16–79 years, N = 983 | TAC, 0.03% or TAC, 0.1% BID for up to 12 weeks | Burning, head/neck area—30% (TAC, 0.03%), 40% (TAC, 0.1%), 19% (VEH) | Pruritus, head/neck area—32% (TAC, 0.03%), 31% (TAC, 0.1%), 29% (VEH) | Tingling, head/neck area—32% (TAC, 0.03%), 5% (TAC, 0.1%), 2% (VEH) |
| Lan et al. [43] | OL, single-arm, multicenter study | Mod-sev AD (Rajka and Langeland criteria; ≥ 10% total BSA), 4–50 years, N = 68 (adult n = 42; pediatric n = 26) | TAC, 0.03% (2–15 years and > 16 years) or 0.1% BID (≥ 16 years) for 4 weeks | Burning b—52.9% (TAC combined group, n = 36) d | Pruritus b—33.8% (TAC combined group, n = 23) d | Most common AEs generally involved local irritation (i.e., burning and stinging) |
| Tan and Langley [47] | OL, noncomparative, multicenter study | Mi-sev AD (Rajka and Langeland criteria), 2–72 years, N = 236 | TAC, 0.1% BID for up to 6 months | Burning c—38.1% (n = 90) | Discontinuation due to burning—0.9% (n = 2) | Erythema/irritation (randomized)—8% (PIM, n = 6), 19% (TAC, n = 13) f |
| Kemper et al. [57] | Multicenter, randomized, parallel-group study | Mod AD (IGA score of 3), 2–17 years, N = 141 | I:1 PIM, 1% vs. TAC, 0.03% BID for up to 6 weeks (randomized); PIM, 1% for 20 weeks (OL) | Warmth/stinging/burning (randomized)—20% (PIM, n = 14), 17% (TAC, n = 12) | Pruritus (randomized)—8% (PIM, n = 6), 20% (TAC, n = 14) | Unspecified ASRs (randomized)—24% (PIM, n = 17), 26% (TAC, n = 18) |
| References            | Study design                   | Patient characteristics | Treatment and duration | Frequency of application site | Frequency of application site | Frequency of application site |
|-----------------------|---------------------------------|-------------------------|------------------------|-----------------------------|------------------------------|------------------------------|
|                       |                                 |                         |                        | burning, stinging, pain, discomfort | pruritus | ASRs (burning/ erythema/pain/ pruritus) |
| Meurer et al. [33]    | Randomized, DB, parallel-group, multicenter study | Mod AD (IGA score of 3; ≥ 5% total BSA), 18–66 years, N = 130 | 1:1 PIM, 1% vs. VEH prn for 24 weeks; TCS for flares; emollients part of both regimens | Burning—45.3% (week 1), 17.2% (week 2), 15.3% (week 4) | Pruritus—41.6% (week 1), 18.8% (week 2), 17.8% (week 4) | ASRs (burning/ erythema/pain/ pruritus) — 14.5% (PIM, n = 9), 8.8% (VEH, n = 6) |
| Won et al. [46]       | OL, noncomparative, multicenter study | Mod-sev AD (Rajka and Langeland’s criteria; ≥ 10% total BSA), 2–57 years, N = 180 | TAC, 0.03% BID for 4 weeks | Burning—45.3% (week 1), 17.2% (week 2), 15.3% (week 4) | Pruritus—41.6% (week 1), 18.8% (week 2), 17.8% (week 4) | ASRs (burning/ erythema/pain/ pruritus) — 14.5% (PIM, n = 9), 8.8% (VEH, n = 6) |
| Paller et al. [58]    | Three prospective, multicenter, randomized, investigator-blinded, comparative studies | Mi-very sev AD (IGADA score; ≥ 5% total BSA), ≥ 2 years, N = 1065 | 1:1 PIM, 1% vs. TAC, 0.03% or 0.1% BID for up to 6 weeks | Burning—10.9% (TAC combined groups, n = 58), 9.6% (PIM, n = 51); significant difference in adults [19.5% (TAC 0.1%, adult group, n = 41)], 11.3% (PIM, n = 23); p = 0.02 | Pruritus—7.0% (TAC combined groups, n = 37), 7.1% (PIM, n = 38) | Local ASRs most common AEs |
| Schachner et al. [44] | Multicenter, randomized, DB, vehicle-controlled study | Mi-mod AD (IGADA score; 2–30% total BSA), 2–15 years, N = 317 | 1:1 TAC, 0.03% vs. VEH BID for up to 6 weeks | Burning/stinging—19.0% (TAC, n = 30), 17.0% (VEH, n = 27) | Pruritus’—23.4% (TAC, n = 37), 33.3% (VEH, n = 53) | Discontinuation due to AS AE—2.5% (TAC), 7.5% (VEH) |
| Eichenfield et al. [28] | Three multicenter, DB, vehicle-controlled studies | Mi-mod AD (IGA score of 2 or 3; ≥ 5% total BSA), 3 months to 17 years, N = 589 | 2:1 PIM, 1% vs. VEH BID for 6 weeks | Burning—9.0% (White, PIM), 5.6% (non-White, PIM), 9.1% (White, VEH), 10.1% (non-White, VEH) | | | |
| References          | Study design            | Patient characteristics          | Treatment and duration                                                                 | Frequency of application site (burning, stinging, pain, discomfort) | Frequency of application site (pruritus) | Frequency of application site (paresthesia, other) |
|--------------------|-------------------------|----------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| Kaufman et al. [25] | Randomized, DB,         | Mi-mod AD (IGA score of 2 or 3; ≥ 5% total BSA), 18–81 years, N = 198                | 1:1 PIM, 1% vs. VEH BID for 7 days, followed by optional 5-week OL extension       | Burning—3.0% (n = 3, PIM) 1.0% (n = 1, VEH)                          | Discontinuation due to burning—1.0% (n = 1, VEH) |                                          |
|                    | parallel-group, vehicle-| control, multicenter study       |                                                                                        |                                                                     |                                        |                                          |
| Lubbe et al. [35]  | OL, single-arm,         | AD of any severity (IGA score), 3 months to 81 years, N = 947                        | PIM, 1% BID for up to 6 months as part of treatment regimen; TCS for flares        | Burning—7.0%                                                          | Pruritus—4.6%, considered treatment-related in 2.9% of patients | Discontinuation due to pruritus—0.1% (n = 1) |
|                    | multicenter, prospective study |                                                |                                                                                        |                                                                     |                                        |                                          |
| Simon et al. [36]  | OL, single-arm,         | AD of any severity (IGA score), 6 months to 70 years, N = 109                        | PIM, 1% BID for up to 6 months, TCS for flares; emollients and antimicrobial agents permitted | Burning—6.4% (n = 7), AE most likely to be considered treatment-related |                                          |                                          |
|                    | multicenter study       |                                                |                                                                                        |                                                                     |                                        |                                          |
| Singalavanija et al. [45] | Multicenter, OL study | Mod-sev AD (Rajka and Langelanda criteria; ≥ 10% total BSA), 2–12 years, N = 61 | TAC, 0.03% BID for up to 4 weeks                                                   | Burning—23% (n = 14)                                              | Pruritus—16.4% (n = 10)                  |                                          |
| Reitamo et al. [49] | Multicenter, noncomparative, phase 3/4 study | AD [none (0.3%), mild (8.2%), moderate (65.5%), severe (26.0%)], 18–85 years, N = 672 | TAC, 0.1% BID for 3 weeks, then QD until clearance, for up to 24 months. TAC BID for 3 weeks in event of flare | Burning—31.7% (n = 213) | Pruritus—113% (n = 76)                  |                                          |
|                    |                         |                                                |                                                                                        |                                                                     |                                        |                                          |
| Remitz et al. [50] | Long-term, OL,          | Mod-sev AD (Rajka and Langelanda criteria), 2–15 years, N = 466                     | TAC, 0.03% or 0.1% BID prn for up to 29.5 months                                    | Burning—28.1% (TAC combined, n = 131), considered treatment-related in 124 patients (26.6%) | Pruritus—30.3% (TAC combined, n = 141), considered treatment-related in 123 patients (26.4%) | Discontinuation due to unspecified AS AEs—3.0% (n = 14) |
| References | Study design | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus | Frequency of application site paresthesia, other |
|------------|--------------|-------------------------|------------------------|---------------------------------------------------------------|----------------------------------------|-----------------------------------------------|
| Murrell et al. [26] | Multicenter, randomized, DB, vehicle-controlled, followed by OL extension study | Mi-mod head and neck (facial) AD (IGA score of 2 or 3), ≥ 12 years, N = 200 | 1:1 PIM, 1% vs. VEH BID for up to 6 weeks (DB); followed by optional PIM BID for up to 6 weeks (OL) | Pain (DB) — 8.9% (PIM, n = 9), 13.1% (VEH, n = 13) | Pruritus (DB) — 8.9% (PIM, n = 9), 5.1% (VEH, n = 5) | Paresthesia (DB) — 4.0% (PIM, n = 4), 3.0% (VEH, n = 3) |
| | | | | Irritation (DB) — 26.7% (PIM, n = 27), 22.2% (VEH, n = 22) | | | Warmth (DB) — 13.9% (PIM, n = 14), 11.1% (VEH, n = 11) |
| | | | | | | Discontinuation due to AS pain/erythema/pruritus/dermatitis (DB) — 4.0% (PIM, n = 4), 4.0% (VEH, n = 4) |
| Fleischer et al. [59] | Prospective, multicenter, randomized, investigator-blinded, comparative study | Mod-very sev AD (IGADA score; ≥ 5% total BSA), ≥ 16 years, N = 281 | 1:1 TAC, 0.1% vs. PIM, 1% BID for up to 6 weeks | Burning — 19.9% (TAC, n = 28), 12.9% (PIM, n = 18) | Pruritus — 7.8% (TAC, n = 11), 5.7% (PIM, n = 8) | Warmth — 2.1% (TAC, n = 3), 0.7% (PIM, n = 1) |
| | | | | Pain — 2.1% (TAC, n = 3), 0.7% (PIM, n = 1) | | | Discontinuation due to AS burning — 0.7% (TAC, n = 1), 0.7% (PIM, n = 1) |
| | | | | | | Discontinuation due to AS pruritus — 0.7% (TAC, n = 1) |
| Zuberbier et al. [29] | Multicenter, DB, randomized, vehicle-controlled, parallel-group study | History of sev AD (Rajka and Langeland score of 8 or 9), 2–17 years, N = 184 | 2:1 PIM, 1% vs. VEH BID for up to 24 weeks; prednicarb ate cream, 0.25% for flares | Skin burning — 1.0% (PIM, n = 2), 1.1% (VEH, n = 1) | | |
| | | | | | | |
| Wollenberg et al. [52] | Multicenter, randomized, vehicle-controlled, phase 3 study | Mi-sev AD (Rajka and Langeland score ≥ 3), ≥ 16 years, N = 257 | TAC, 0.1% BID for up to 6 weeks (OL period), followed by TAC, 0.1% or VEH QD twice weekly for 12 months (DB period); TAC, 0.1% applied BID for up to 6 weeks during DB period if disease exacerbation | Irritation — 32.3% (n = 83, OL) | Pruritus — 17.9% (TAC, n = 46, OL) | Warmth — 7.0% (TAC, n = 18, OL) |
| | | | | Irritation — 5.2% (TAC, n = 6, DB); 6.5% (VEH, n = 7, DB) | Pruritus — 11.2% (TAC, n = 25, DB); 11.1% (VEH, n = 12, DB) | |
| References          | Study design          | Patient characteristics | Treatment and duration                                                                                                                                                                                                 | Frequency of application site                                                                                                                                 |
|--------------------|-----------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zuberbier and Brautigam [30] | Multicenter, randomized, DB, parallel-group, vehicle-controlled, multicenter study | Mi-mod facial AD (IGA score of 1–3), 2–17 years, N = 140 | 1:1 PIM, 1% or VEH BID for up to 24 weeks; prednicarbate cream, 0.25% for flares                                                                                                                                 | Burning — 1.3% (PIM, n = 1), 1.6% (VEH, n = 1)                                                                                                               |
| Sigurgeirsson et al. [31] | Multicenter randomized, DB, parallel-group, comparative, vehicle-controlled study | History of mi-mod AD (IGA score of 2 or 3), 2–17 years, N = 521 | 1:1 PIM, 1% vs. VEH BID for up to 26 weeks; TCS for flares                                                                                                                                                          | Burning — 1.2% (PIM, n = 3), 3.1% (VEH, n = 8)                                                                                                            |
| Thaci et al. [53]    | Multicenter, randomized, vehicle-controlled, phase 3 study | Mi-sev AD (Rajka and Langeland score ≥ 3), 2–15 years, N = 267 | TAC, 0.03% BID for up to 6 weeks (OL period), followed by TAC, 0.03% or VEH QD twice weekly for 12 months (DB period); TAC, 0.1% applied BID for up to 6 weeks during DB period if disease exacerbation | Irritation — 6.0% (TAC, n = 16, OL)                                                                                                                             |
| Ring et al. [37]     | Multicenter, naturalistic, OL study | Mi-mod AD (IGA score ≥ 1), ≥ 3 months, N = 2034 | PIM, 1% BID for up to 12 months, TCS for flares                                                                                                                                                                         | Burning — 6.8%                                                                                                                                             |

ASRs were most common events leading to discontinuations in both groups.
| References | Study design | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus | Frequency of application site paresthesia, other |
|------------|--------------|--------------------------|------------------------|-------------------------------------------------|---------------------------------|---------------------------------|
| Paller et al. [56] | Randomized, 2-phase, multicenter study | Mod-sev AD (PSGA score ≥ 3), 2–15 years, N = 206 | Phase 1 acute (DB): 1:1 TAC, 0.03% vs. alclometasone ointment, 0.05% for 4 days Phase 1 short-term (OL): TAC, 0.03% BID for up to 16 weeks Phase 2 (DB): 1:1 TAC, 0.03% vs. VEH, QD 3 times/week for up to 40 weeks Phase 2 relapse (OL): TAC, 0.03% BID for up to 8 weeks | Burning—9.2% (TAC, n = 9, phase 1 acute, DB), 8.7% (alclometasone, n = 9, phase 1 acute, DB); 12.2% (TAC, n = 12, phase 1 short-term, OL, week 2), 9.7% (alclometasone/TAC, n = 10, phase 1 short-term, OL, week 2); 2.9% (TAC, n = 2, phase 2, DB), 2.8% (VEH, n = 1, phase 2, DB); 2.7% (TAC, n = 2, phase 2 relapse, OL) | Pruritus—6.1% (TAC, n = 6, phase 1 acute, DB), 3.9% (alclometasone, n = 4, phase 1 acute, DB); 6.1% (TAC, n = 6, phase 1 short-term, OL, week 2), 9.7% (alclometasone/TAC, n = 10, phase 1 short-term, OL, week 2); 1.5% (TAC, n = 1, phase 2, DB), 5.6% (VEH, n = 2, phase 2, DB); 0% (TAC, n = 0, phase 2 relapse, OL) |
| Langley et al. [39] | OL extension study of 2 multicenter, randomized, DB, phase 3 studies | Mi-mod AD (IGA score of 2 or 3; ≥ 5% total BSA), 2–17 years, N = 403 | 2:1 PIM, 1% vs. VEH for 6 weeks (DB), followed by PIM, 1% BID for 20 weeks (OL) | Burning—10.5% (PIM, DB), 13.2% (VEH, DB), 2.6% (PIM/PIM, PIM, OL), 2.0% (VEH/PIM, OL) |
| References                  | Study design                | Patient characteristics | Treatment and duration | Frequency of application site | Frequency of application site | Frequency of application site |
|-----------------------------|-----------------------------|-------------------------|------------------------|-------------------------------|-------------------------------|-------------------------------|
| Abramovits et al. [60]      | Multicenter, prospective, randomized, investigator-blinded, comparative study | Mod AD (IGADA score; ≥ 5% total BSA), ≥ 16 years, N = 188 (TAC, n = 8; PIM, n = 90) | 1:1 TAC, 0.1% vs. PIM, 1% BID for up to 6 weeks | Burning—19.4% (TAC, n = 19), 13.3% (PIM, n = 12) | Pruritus—9.2% (TAC, n = 9), 5.6% (PIM, n = 5) | Warmth—2.0% (TAC, n = 2), 1.1% (PIM, n = 1) |
| Reitamo et al. [51]         | Multicenter, noncomparative, OL study | AD (5–60% total BSA for ages 2–15 years and ≥ 5% total BSA for ages ≥ 16 years), 2–72 years, N = 782 | TAC, 0.1% BID for up to 48 months | Burning—37.3% (n = 292) | Pruritus—15.9% (n = 124) | Most frequent ASRs were skin burning and pruritus |
| Breneman et al. [55]        | Randomized, multicenter study | Mod-sev AD (PSGA score ≥ 3), ≥ 2 years, N = 383 | Phase 1 acute (DB): 1:1 TAC, 0.03% or 0.1% vs. alclometasone ointment, 0.05% for 4 days | Burning—10.1% (TAC, n = 19, phase 1 acute, DB), 5.3% (alclometasone, n = 10, phase 1 acute, DB); 12.2% (TAC, n = 23, phase 1 short-term, OL), 8.5% (alclometasone/TAC, n = 16, phase 1 short-term, OL); 1.6% (TAC, n = 2, phase 2, DB), 1.4% (VEH, n = 1, phase 2, DB); 3.2% (TAC, n = 4, phase 2 relapse, OL) | Pruritus—6.4% (TAC, n = 12, phase 1 acute, DB), 2.6% (alclometasone, n = 5, phase 1 acute, DB); 7.4% (TAC, n = 14, phase 1 short-term, OL), 9.0% (alclometasone/TAC, n = 17, phase 1 short-term, OL); 0.8% (TAC, n = 1, phase 2, DB), 2.8% (VEH, n = 2, phase 2 DB); 0.8% (TAC, n = 1, phase 2 relapse, OL) | Irritation—0% (TAC, n = 0, phase 1 acute, DB), 0.5% (alclometasone, n = 1, phase 1 acute, DB); 0% (TAC, n = 0, phase 1 short-term, OL), 1.1% (alclometasone/TAC, n = 2, phase 1 short-term, OL); 1.6% (TAC, n = 2, phase 2, DB), 0% (VEH, n = 0, phase 2, DB); 0% (TAC, n = 0, phase 2 relapse, OL) |
| References         | Study design                      | Patient characteristics | Treatment and duration                                                                 | Frequency of application site | Frequency of application site | Frequency of application site |
|--------------------|-----------------------------------|-------------------------|-----------------------------------------------------------------------------------------|-----------------------------|-----------------------------|-------------------------------|
| De Backer et al. [38] | Multicenter, single-arm, observational, OL study | Mi-mod AD (IGA score), ≥ 2 years, *N* = 416 | PIM, 1% BID prn for up to 1 year; emollients and TCS permitted | burning, stinging, pain, discomfort | pruritus | ASRs (burning, irritation, erythema, pruritus, stinging, pain, paresthesia; vesicular eruption) | 46.5% of AEs, 95% considered treatment-related, 50% mild, 35% moderate, 15% severe |
| Hoeger et al. [27] | Randomized, DB, multicenter study; followed by 6-week OL extension | Mi-mod facial AD (IGA score of 2 or 3), 2–11 years, *N* = 200 | 1:1 PIM, 1% vs. VEH BID to the face, head, and neck and prn to other affected areas for up to 6 weeks, followed by PIM, 1% BID prn to all affected areas for up to 6 weeks | Irritation—5.1% (PIM, *n* = 5, DB), 5.0% (VEH, *n* = 5, DB) | Discontinuation due to irritation—0.3% (PIM, *n* = 1, OL) | Discontinuation due to pruritus—0.3% (PIM, *n* = 1, OL), treatment-related; 0.7% (PIM BID, *n* = 1, DB) |
| Ruer-Mulard et al. [40] | Multicenter OL study; followed by randomized, DB, multicenter study | Mi-sev AD (IGA score ≥ 2; ≥ 5% total BSA), 2–17 years, *N* = 300 | PIM, 1% BID for up to 6 weeks (OL), followed by 1:1 PIM, 1% BID vs. PIM, 1% QD for up to 16 weeks (DB); TCS permitted for disease exacerbation | Discontinuation due to pruritus—0.0% (PIM ? TCS, *n* = 2), 0.6% (VEH ? TCS, *n* = 1) | Burning—9.9% (TAC combined, *n* = 17), 14.2% (PIM, *n* = 25) | Pruritus—7.0% (TAC combined, *n* = 12), 10.2% (PIM, *n* = 18), 0% (PIM, *n* = 0) |
| Kirsner et al. [61] | Three prospective, multicenter, randomized, comparative studies | Mi-very sev AD (IGADA score; ≥ 5% total BSA), ≥ 2 years, *N* = 347 | 1:1 PIM, 1% BID vs. TAC, 0.03% or 0.1% BID for up to 6 weeks | Burning—4.1% (TAC combined, *n* = 7), 1.7% (PIM, *n* = 3) | Pain—4.1% (TAC combined, *n* = 7), 1.7% (PIM, *n* = 3) | Warmth—1.2% (TAC combined, *n* = 2), 0.0% (PIM, *n* = 0) |
| Meurer et al. [23] | Randomized, multicenter, parallel-group, vehicle-controlled study | Sev AD (IGA score ≥ 40; ≥ 5% total BSA, excluding the face), 2–17 years, *N* = 376 | 1:1 PIM, 1% and TCS (FP, 0.05% or HA, 1% for the face, neck, and intertriginous areas) vs. VEH and TCS BID for 4 weeks followed by 12 weeks of observation period in which no drug was administered | Burning—1.6% (PIM + TCS, *n* = 3), 1.4% (VEH + TCS, *n* = 2) | Exacerbation of pruritus—0.0% (PIM + TCS, *n* = 2), 0.6% (VEH + TCS, *n* = 1) | |
| References       | Study design                  | Patient characteristics | Treatment and duration | Frequency of application site                                                                 | Frequency of application site | Frequency of application site |
|------------------|-------------------------------|-------------------------|------------------------|------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|
| Reitamo et al.   | Two randomized, multicenter,  | Mod-sev AD (Rajka and   | TAC, 0.03% or 0.1% BID for up to 6 weeks (OL), followed by 1:1 TAC, 0.03% or 0.1% vs. VEH, QD twice/week for up to 12 months (DB); TAC, 0.03% or 0.1% BID for up to 6 weeks in the event of a flare during the DB period | Irritation—a— | Pruritus—a— | ASRs were most common treatment-related AEs in OL and DB phases |
| [54]             | comparative, phase 3 studies  | Langeland criteria)     |                        |                                                                                                  | 11.3% (TAC, n = 9, adults, DB), 10.3% (TAC, n = 8, children, DB), 12.3% (VEH, n = 9, adults, DB), 10.7% (VEH, n = 8, children, DB) | 5.0% (TAC, n = 4, adults, DB), 3.8% (TAC, n = 3, children, DB), 8.2% (VEH, n = 6, adults, DB), 13.3% (VEH, n = 1, children, DB) |

AD: atopic dermatitis, AE: adverse event, AS: application site, ASR: application site reaction, BID: twice daily, BSA: body surface area, DB: double blind, HA: hydrocortisone acetate cream, FP: fluticasone propionate cream, IGA: Investigator’s Global Assessment, IGADA: Investigator’s Global Atopic Dermatitis Assessment, Mm: mild, Mm: moderate, OL: open label, PIM: pimecrolimus cream, prn: as needed, PSGA: Physician’s Static Global Assessment, QD: once daily, Sev: severe, TAC: tacrolimus ointment, VEH: vehicle

a Rajka and Langeland AD severity criteria are detailed in [88]
b Among most common TEAEs
c Among most common treatment-related TEAEs or application site reactions
d Not specified if application site event
e Considered related to treatment
f Significant difference from vehicle or active comparator in frequency
was more common in children with moderate than mild AD (29.5% vs. 12.4%, \( p = 0.008 \)). Two of the five studies described severity and timing of AS tolerability issues, describing AS burning, stinging, and tingling as mild to moderate and transient [42], and AS burning and pruritus as resolving within the first week of treatment [45]. Ten tacrolimus studies involved long-term therapy (6–29.5 months), of which five were open label [47–51] and five included both double-blind and open-label phases [52–56]. Among five long-term studies providing overall rates or for which overall rates could be calculated, rates of AS burning/irritation and pruritus ranged from 4.4% to 43.7% and 10.7% to 33.9%, respectively, in tacrolimus-treated patients versus 4.7% and 11.5% in vehicle-treated patients. Seven long-term studies indicated that burning, irritation, and/or pruritus were among the most common AEs and/or treatment-related AEs [48–54], and five studies specified that burning and/or pruritus events were generally mild to moderate and/or decreased in prevalence over time [47–51].

Five studies directly compared tacrolimus ointment, 0.03% or 0.1% to pimecrolimus cream, 1% and all evaluated short-term treatment (up to 6 weeks) [57–61]. Four of these studies indicated that AS burning and pruritus were among the most common AEs in TCI-treated patients [58–61]. Kempers et al. [57] reported a significantly greater rate (\( p = 0.039 \)) of AS erythema/irritation in tacrolimus-treated children with moderate AD (19%) than in pimecrolimus-treated children (8%) and a trend toward a higher rate of AS pruritus in the tacrolimus group, but this finding was not significant (\( p = 0.073 \)) [57]. Although incidence of local AEs generally decreased over time, AS erythema/irritation and warmth/burning/stinging events were more likely (\( p < 0.001 \)) to last more than 30 min in tacrolimus-treated than pimecrolimus-treated children. Another study [58] reported a higher rate (\( p = 0.02 \)) of AS burning in tacrolimus-treated adults with mild to severe AD (19.5%) than in pimecrolimus-treated adults (11.3%). Significance was driven by a greater rate of burning in tacrolimus-treated patients (11.4% vs. 4.9%) in the first week of treatment, after which rates were comparable. These differences may be a result of greater skin penetration of tacrolimus compared with pimecrolimus [62].

**TOLERABILITY OF TCSs**

Among the 11 included trials of TCSs, overall prevalence rates of burning, pruritus, irritation, or warmth in TCS-treated patients ranged from less than 1% to 6% (Table 2). Three studies evaluated fluticasone propionate (FP), 0.05% cream [20, 63] or lotion [64]. Eichenfield et al. [64] reported burning/stinging in 1.8% of children and adults with moderate to severe AD receiving up to 1 month of treatment with FP lotion (vehicle, 1.4%), and pruritus in 0.5% of FP-treated patients (vehicle, 0.5%). Both events were considered possibly related to treatment, but the authors did not specify whether the events were AS-specific. An open-label study of 3–4 weeks of treatment with FP cream in children with moderate to severe AD reported AS burning that resolved within 1 day in 2.0% of patients [20]. Another study comparing up to 4 months of treatment with FP cream to hydrocortisone cream (HC), 1% or hydrocortisone butyrate (HCB) cream, 0.1% in children with moderate to severe AD reported no AS tolerability issues in FP- or HC-treated patients and AS pruritus in 3.2% of HCB-treated patients [63]. Other included trials of HCB involved 4 weeks of application of HCB lipocream, 0.1% [65] or lotion, 0.1% [66] in children and adolescents with mild to moderate AD and reported numerically lower rates of AS tolerability issues (1% each for burning [66] and irritation [65], respectively).

Two studies investigated 4 weeks of treatment with desonide, 0.05% in children and adolescents with mild to moderate AD, testing either the hydrogel [19] or the foam [67] formulation. Burning was among the most common AS AEs for both formulations, occurring in 1% (hydrogel) and 3% (foam vs. 7% in vehicle group, \( p = 0.004 \)) of patients. In both studies, AS pruritus occurred in less than 1% of desonide-treated patients.

Long-term treatment (4–6 months) with mometasone furoate (MF) fatty cream, 0.1% [68]
| References       | Study design                              | Patient characteristics                                                                 | Treatment and duration                                                                 | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|------------------|-------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------|
| Faergemann et al. [68] | Multicenter, OL study                      | AD [combined assessment score rating erythema, infiltration, and lesion number from 0 (none) to 3 (severe) ≥ 7], 17–63 years, N = 68 | MF fatty cream, 0.1% twice weekly for 6 months following run-in period of MF fatty cream, 0.1% QD for 3 weeks |                                                                  |                                               | Warmth<sup>a</sup> — 1.5% (n = 1)               |
| Cato et al. [70]   | Multicenter, randomized, DB, active and vehicle-controlled study | AD [total score rating erythema, induration, and pruritus each from 0 (absent) to 6 (markedly severe) ≥ 7 for ≥ 2 of 3 test lesions], 18–86 years, N = 150 | 1:1:1 TA vs. TNX vs. VEH BID for 2 weeks |                                                                  |                                               | Local burning, pruritus, or disease exacerbation<sup>b</sup> — 6% (n = 3, TNX), 4% (n = 2, TA), 12% (n = 6, VEH) |
| References  | Study design                      | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|-------------|-----------------------------------|-------------------------|------------------------|---------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Paller et al. [71] | Multicenter, randomized, DB, vehicle-controlled study (study 1); multicenter, OL, cortisol-stimulation study (study 2); OL, allergen reactivity study (study 3) | AD [≥ 20% total BSA (study 1), ≥ 50% total BSA (study 2), ≥ 20% total BSA with confirmed peanut allergy (study 3)]; 2–12 years; N = 94 (study 1), N = 32 (study 2), N = 9 (study 3) | FA in peanut oil, 0.01% or peanut oil VEH BID to areas other than the face and intertriginous sites for 2 weeks followed by FA in peanut oil, 0.01% BID for 2 weeks, followed by peanut oil VEH BID for 2 weeks (study 1); FA in peanut oil, 0.01% BID for 4 weeks over ≥ 50% BSA (study 2); FA in peanut oil, 0.01% or peanut oil VEH prick and patch testing then FA in peanut oil, 0.01% BID to areas other than the face for 1 week (study 3) | Mild itching and burning—3.1% (n = 1, FA, study 2) |
Table 2 continued

| References       | Study design                      | Patient characteristics                                                                 | Treatment and duration                                                                 | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|------------------|-----------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Friedlander et al. [20] | Phase 4, multicenter, OL safety study | Mod-sev AD [total severity score $\geq 6.0$ for any 3 of 8 signs/symptoms (erythema, pruritus, papulation, induration, oozing/crusting, scaling, excoriation, lichenification) rated from 0 (absent) to 3 (severe); $\geq 35\%$ total BSA, excluding diaper area, eyelids, perioral area, nostrils, and TCS contraindicated locations], 3 months to 5 years, 11 months, $N = 51$ | FP cream, 0.05% BID to all lesions except diaper area, eyelids, perioral area, nostrils, and TCS contraindicated locations for up to 4 weeks | Burning$^a$ $-2.0\%$ ($n = 1$) | | |

$^a$ Reducing dose: $2.0\%$ ($n = 1$)
| References     | Study design                               | Patient characteristics                                                                 | Treatment and duration                                                                 | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|----------------|--------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------|
| Kirkup et al.  | Two multicenter, randomized, DB, parallel-group studies | Mod-sev AD flare with total AD score [no. of affected body areas (max 12) + sum of erythema, excoriation, and lichenification scores (each rated from mild (0) to severe (3)) for the target area (defined as particularly troublesome site; max score = 9)] ≥ 6 (max = 21); 2–14 years; N = 137 (study 1), N = 128 (study 2) | FP cream, 0.05% or HC cream, 1% BID for 2–4 weeks then prn (up to BID) for 3 months (study 1); FP cream, 0.05% or HCB cream, 0.1% BID for 2–4 weeks then prn (up to BID) for 3 months (study 2); emollients permitted | Pruritus\(^a\) — 3.2% (n = 2, HCB, study 2) |                                                      |
| Eichenfield et al. [64] | Two multicenter, randomized, DB, vehicle-controlled studies | Mod-sev AD (Rajka and Langeland\(^c\) score > 4), 3 months to 87 years, N = 438 | FP lotion, 0.05% or VEH QD for 4 weeks to affected areas except the eyelids, perioral area, nostrils, and diaper area | Burning/stinging\(^a,d\) — 1.8% (n = 4, FP), 1.4% (n = 3, VEH) | Pruritus\(^a,d\) — 0.5% (n = 1, FP), 0.5% (n = 1, VEH) |                                                      |
| References      | Study design                                      | Patient characteristics                                                                 | Treatment and duration                                                                 | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|-----------------|--------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Hebert et al.   | Two phase 3, randomized, DB, vehicle-controlled studies | Mi-mod AD (IGSS score; ≥ 10% total BSA), 3 months to 18 years, N = 582                  | Desonide hydrogel, 0.05% or VEH BID for 4 weeks                                        | Burning — 1% (desonide), not stated (VEH)                        | Pruritus — 1% (desonide), not stated (VEH) | AS events (unspecified) — 3% (desonide), incident rate not higher than VEH |
| Matheson et al. [66] | Multicenter, randomized, DB, parallel-group, vehicle-controlled study | Mi-mod AD (PGA score of 2 or 3; ≥ 10% total BSA), 3 months to < 18 years, N = 284      | 1:1 HCB lotion, 0.1% vs. VEH BID for 4 weeks                                            | Burning — 1% (n = 1, HCB), 6% (n = 8, VEH)                      | Pruritus — not stated (HCB), 3% (VEH)        |                                                               |
| Peserico et al. [69] | Multicenter, randomized, DB, vehicle-controlled, parallel-group study | 2-year history of moder-sev AD with severe or very severe acute flare (IGA ≥ 4), ≥ 12 years, N = 249 | MPA cream, 0.1% QD + emollient for up to 4 weeks (acute, OL) then 1:1 MPA, 0.1% QD twice weekly + emollient BID 5 times weekly: emollient BID, for 16 weeks (maintenance, DB) | Burning — 1% (n = 1; MPA, during entire study) |                                                               |                                                               |
Table 2 continued

| References       | Study design                          | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|------------------|---------------------------------------|-------------------------|------------------------|------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Hebert et al.    | One phase 2, multicenter, OL HPA axis | Mi-mod AD (ISGA score of 2 or 3; ≥ 25% total treatable BSA); one phase 2 safety/efficacy study, and one phase 3 safety/efficacy study, N = 81 (phase 2 OL), N = 768 (3 combined efficacy studies) | Desonide foam, 0.05% BID for 4 weeks (OL), 2:1 desonide vs. VEH BID for 4 weeks (combined safety/efficacy studies) | Burning (combined safety/efficacy studies) — 3% (n = 14, desonide), 7% (n = 16, VEH)
| HCB lipocream, 0.1% or vehicle BID for up to 1 month | Pruritus (combined safety/efficacy studies) — 0% (n = 2, desonide), 0% (n = 0, VEH) |
| Abramovits et al. [65] | Phase 3, multicenter, randomized, DB, vehicle-controlled study | Mi-mod AD (PGA score of 2 or 3; ≥ 10% total BSA); 3 months to < 18 years, N = 264 | HCB lipocream, 0.1% or vehicle BID for up to 1 month | Irritation — 1% (n = 1, HCB), 0% (n = 0, VEH) |

AD: atopic dermatitis, AE: adverse event, AS: application site, ASR: application site reaction, BID: twice daily, BSA: body surface area, DB: double blind, FA: fluocinolone acetonide, FP: fluticasone propionate, HC: hydrocortisone, HCB: hydrocortisone butyrate, IGA: Investigator’s Global Assessment, IGSS: Investigator’s Global Severity Score, ISGA: Investigator’s Static Global Assessment, Mi: mild, Mo: moderate, MF: mometasone furoate, MPA: methylprednisolone aceponate, OL: open label, PGA: Physician Global Assessment, prn: as needed, QD: once daily, Sev: severe, TA: triamcinolone acetonide, TNX: triamcinolone acetonide–laurocapram, VEH: vehicle

- Considered treatment-related or possibly treatment-related
- Among most common TEAEs
- Rajka and Langeland AD severity criteria are detailed in [88]
- Not specified if application site event
- Among most common treatment-related TEAEs or application site reactions
- Significant difference from vehicle or active comparator in frequency
or methylprednisolone aceponate (MPA) cream, 0.1% [69] was associated with relatively low rates of tolerability issues. AS warmth was reported in 1.5% of adult patients treated with MF cream, and MPA-related burning occurred in less than 1% of adolescent and adult patients with an acute flare of moderate to severe AD.

The remaining TCS trials evaluated triamcinolone acetonide (TA) [70], triamcinolone acetonide–laurocapram (TNX) [70], and fluocinolone acetonide (FA), 0.01% in peanut oil [71]. A study of 2 weeks of treatment with TA, TNX, or vehicle in adults with AD reported rates of AS burning, pruritus, or disease exacerbation of 4% (TA), 6% (TNX), and 12% (vehicle) [70]. These were the highest rates of AS tolerability issues reported among TCS studies but may reflect the fact that all AS reactions were reported together. Mild AS itching and burning (3.1%) were reported during a 4-week open-label trial of FA in children with AD (study 2 of three trials reported in [71]).

TOLERABILITY FINDINGS FROM HEAD-TO-HEAD COMPARISONS OF TCIs and TCSs

Nine studies directly compared TCIs to TCSs, of which four reported significantly greater rates of AS burning, pruritus, or tingling in TCI treatment groups (Table 3) [72–80]. Luger et al. [72] compared up to 1 year of combination TCS therapy with TA cream, 0.1% and hydrocortisone acetate (HA) cream, 1% to TCI therapy with pimecrolimus cream, 1%. AS tolerability issues were numerically more frequent with pimecrolimus (burning, 25.9%; pruritus, 5.5%) than TA/HA combination therapy (burning, 10.9%; pruritus, 1.8%), and AS issues were mild to moderate, resolved within 7 days, and occurred early in treatment.

Three studies compared tacrolimus ointment (0.1% and/or 0.03%) to HA ointment, 1% over a 3-week treatment period in children/adolescents and reported a range of tolerability issues [73–75]. For twice-daily treatment, rates of skin burning across studies for tacrolimus, 0.03%, tacrolimus, 0.1% and HA ranged from 18.5% to 23.8%, 20.4%, and 3.3% to 14.5%, respectively. A study with 3.3% rate of burning in HA patients did not indicate whether burning sensation was AS-specific. Rates of AS pruritus across studies ranged from 10.0% to 21.4% (tacrolimus, 0.03%), 11.3% (tacrolimus, 0.1%), and 3.3% to 15.9% (HA). Two of the three studies [73, 74] reported significantly greater rates ($p < 0.05$) of AS burning in tacrolimus-treated children and adolescents with moderate to severe AD compared with the HA group. Both studies reporting significant differences indicated that tolerability issues were predominantly mild to moderate and decreased in prevalence over the 3 weeks of treatment, with highest rates observed on days 1–4.

Two studies compared tacrolimus to HCB ointment, 0.1% in adults with moderate to severe AD, reporting more tolerability issues in TCI than TCS treatment groups. Reitamo et al. [76] compared up to 6 months of therapy with 0.1% HCB and 1% HA to tacrolimus (TAC), 0.1% and reported significantly greater rates of skin tingling (TCS, 0.6%; TAC, 2.7%; $p = 0.02$) and burning (TCS, 13.8%; TAC, 52.4%; $p < 0.001$) in the tacrolimus treatment group than in the TCS group. Another study by Reitamo et al. [78] compared 3 weeks of therapy with HCB, 1% to tacrolimus, 0.03% or 0.1% and reported significantly greater rates of AS burning [Table 3; HCB, 12.9%; TAC (0.03%), 45.1%; TAC (0.1%), 59.2%; $p < 0.05$ for TAC treatments vs HCB] and pruritus [Table 3; HCB, 9.7%; TAC (0.03%), 20.2%; TAC (0.1%), 15.2%; $p < 0.05$ for TAC treatments vs HCB] in tacrolimus-treated patients. Tolerability issues decreased in prevalence over time in both studies. The highest rates of AS burning and pruritus events were observed on days 1–4 in the 3-week study, and the highest AS burning rates were observed during the first week of the 6-month study.

Two studies compared short-term (3–6 weeks) treatment with fluticasone ointment, 0.005% to tacrolimus (0.03% or 0.1%), and reported an overall pattern of more tolerability issues in tacrolimus than in fluticasone treatment groups. Doss et al. [79] reported a higher rate of AS skin burning sensation in tacrolimus-treated patients (TAC 0.03%, 7.6%; fluticasone, 2.5%) that contributed to a significant difference in frequency of unspecified AS AEs (TAC 0.03%,
18.0%; fluticasone, 11.3%; \( p = 0.038 \) between the two treatment arms during the first 3 weeks of the study. Another study by Doss et al. [80] reported rates of AS burning and pruritus specific to facial and nonfacial areas (see Table 3 for full list) that were numerically higher in the tacrolimus, 0.1% group than in the fluticasone group for facial areas but not significantly different.

Bieber et al. [77] compared 3 weeks of treatment with MPA ointment, 0.1% to tacrolimus, 0.03% in children with severe or very severe acute AD flares, showing a numerically higher incidence of AEs in the tacrolimus group (4.4%) than in the MPA group (0%), with the tacrolimus-treated patients reporting these events as pruritus, erythema, skin burning, and hot flushes.

Taken together, studies directly comparing TCIs with TCSs suggest that AS tolerability issues are more common with TCI treatment than with TCS treatment but tend to decrease over time. This may be related to improved skin barrier function resulting in lower skin penetration with continued use [81]. However, definitive conclusions are limited by differences in study design and reporting of events. Furthermore, literature reporting comparisons of pimecrolimus to TCS therapy is very limited.

**TOLERABILITY OF CRISABOROLE**

In two identically designed, 4-week phase 3 trials (studies AD-301 and AD-302) of crisaborole ointment, 2% in AD patients at least 2 years of age with mild to moderate AD, most treatment-related AEs involved AS pain (defined as burning or stinging), which was reported in 4.4% of crisaborole-treated patients and 1.2% of vehicle-treated patients (Table 4; pooled data, \( p = 0.001 \)) [21]. Most patients (76.7%) experiencing AS pain reported the AE on the first day of treatment, and most (77.6%) reported resolution within 1 day of onset. In a 48-week open-label, single-arm safety extension trial (study AD-303), treatment-related AS pain was reported in 2.3% of crisaborole-treated patients (\( n = 12 \); onset in AD-301/AD-302, \( n = 6 \); onset in AD-303, \( n = 6 \)) [22]. AS pain events in crisaborole-treated patients enrolled in AD-303 had a median duration of 5 days, and 33% resolved within 1 day of onset.

**POTENTIAL STRATEGIES FOR MANAGING TOLERABILITY ISSUES ASSOCIATED WITH TOPICAL TREATMENTS FOR AD**

AS tolerability issues were observed for all three drug classes in this analysis, underscoring the need for mitigation strategies in affected patients. Accordingly, American Academy of Dermatology (AAD) and American Academy of Allergy, Asthma & Immunology (AAAAI) guidelines recommend patient counseling, whereby physicians advise patients to anticipate transient burning and stinging with TCI application [10, 11]. AAD, AAAAI, and European Academy of Dermatology and Venereology (EADV) guidelines also recommend integration of regular emollient use into AD treatment plans to maintain skin barrier function, alleviate symptoms of AD, and reduce irritation [10–12]. Emollients improve signs and symptoms of AD while demonstrating good tolerability [82]. However, skin stinging/burning and pruritus have been reported in trials of some emollient formulations [15–18]; therefore, the optimal moisturizer should be devoid of ingredients that are irritating or sensitizing to the patient [83]. In the case of an acute AD flare, AAD [10] and EADV [12] guidelines suggest preceding TCI treatment with TCS treatment to restore skin barrier function so that large molecules (larger than 500 Daltons such as pimecrolimus and tacrolimus) cannot easily penetrate the skin (i.e., the 500-Dalton rule) [84], thereby minimizing TCI-associated AS tolerability issues [10, 12].

Additional published recommendations suggest administering oral aspirin [85]. A small retrospective study reported that 500 mg oral aspirin taken 1 h before initial tacrolimus reaplication reduced to mild (\( n = 3 \)) or prevented (\( n = 3 \)) burning as assessed during follow-up interviews by six adult patients who had discontinued tacrolimus because of severe burning [85]. Potential mediators of the anti-burning effect of aspirin are inhibition of
| References       | Study design                     | Patient characteristics                      | Treatment and duration | Frequency of application site discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|------------------|----------------------------------|---------------------------------------------|------------------------|------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Reitamo et al.   | Phase 3, comparative, multicenter, DB, parallel-group study | Mod-sev AD (Rajka and Langeland criteria; ≥ 5% total BSA), 16–70 years, N = 570 | 1:1:1 TAC, 0.03% vs. TAC, 0.1% vs. HCB ointment, 0.1% BID for 3 weeks | Burning—12.9% (n = 24, HCB), 59.2% (n = 113, TAC, 0.1%), 45.1% (n = 87, TAC, 0.03%) | Pruritus—9.7% (n = 18, HCB), 15.2% (n = 29, TAC, 0.1%), 20.2% (n = 39, TAC, 0.03%) | Discontinuation due to serious, treatment-related AS burning and pruritus—0.5% (n = 1, TAC 0.1%) |
| Reitamo et al.   | Phase 3, comparative, multicenter, randomized, DB, parallel-group study | Mod-sev AD (Rajka and Langeland criteria; ≥ 5–60% total BSA), 2–15 years, N = 560 | 1:1:1 TAC, 0.03% vs. TAC, 0.1% vs. HA ointment, 0.1%, BID for up to 3 weeks | Burning—7% (HA, n = 13), 18.5% (TAC, 0.03%, n = 35), 20.4% (TAC, 0.1%, n = 38) | Pruritus—7.6% (HA, n = 14), 13.2% (TAC, 0.03%, n = 25), 11.3% (TAC, 0.1%, n = 21) | Discontinuation due to skin burning and pain—0.5% (TAC, 0.03%, n = 1) |
| Reitamo et al.   | Randomized, DB, multicenter comparative study | Mod-sev AD (Rajka and Langeland criteria; ≥ 5% total BSA), 2–15 years, N = 624 | 1:1:1 TAC, 0.03% QD vs. TAC, 0.03% BID vs. HA ointment BID for 3 weeks | Burning—14.5% (n = 30, HA), 23.2% (n = 48, TAC QD), 23.8% (n = 50, TAC BID) | Pruritus—15.9% (n = 33, HA), 18.4% (TAC QD, n = 38), 21.4% (TAC BID, n = 45) | Discontinuation due to burning—0.5% (n = 1, TAC BID) |
| Luger et al.     | Multicenter, randomized, DB, parallel-group study | Mod-sev AD (Rajka and Langeland criteria; ≥ 5% total BSA), 18–79 years, N = 658 | 1:1 PIM, 1% vs. TA cream, 0.1% (trunk/limbs) and HA cream, 1% (face, neck, intertriginous areas), BID for up to 1 years | Burning—25.9% (PIM, n = 85), 10.9% (TA + HA, n = 36) | Pruritus—5.5% (PIM, n = 18), 1.8% (TA + HA, n = 6) | Discontinuation due to ASR (unspecified)—7.6% (PIM), 0.9% (TA + HA) |

ASRs (unspecified) were the AEs most likely to lead to discontinuation in both groups.
Table 3 continued

| References  | Study design | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|-------------|--------------|------------------------|------------------------|---------------------------------------------------------------|---------------------------------|---------------------------------|
| Reitamo et al. [76] | Randomized, DB, comparative, multicenter, phase 3 study | Mod-sev AD (Rajka and Langeland score ≥ 4.5), ≥ 18 years, N = 972 | 1:1 TAC, 0.1% vs. HCB ointment, 0.1% (trunk/limbs) and HA ointment, 1% (head/neck), BID for up to 6 months | Burning — 13.8% (HCB + HA, n = 67), 52.4% (TAC, n = 255) | Pruritus — 13.4% (HCB + HA, n = 65), 18.1% (TAC, n = 88) | Skin tingling — 0.6% (HCB + HA, n = 3), 2.7% (TAC, n = 13) |
| Bieber et al. [77] | Randomized, DB, comparative, multicenter study | Sev-very sev flare of AD (IGA score ≥ 4), 2–15 years, N = 265 | 1:1 MPA ointment, 0.1%, QD vs. TAC, 0.03% BID for up to 3 weeks | Incidence of treatment-related AEs (unspecified) — 0% (MPA, n = 0), 4.4% (TAC, n = 6, pruritus, erythema, skin burning, and hot flushes) | Discontinuations due to AEs — 0% (MPA, n = 0), 2.9% [TAC, n = 4, treatment-related pruritus (n = 1), treatment-related pruritus/skin burning (n = 1), treatment-related pruritus/hot flushes (n = 1), scarlet fever (n = 1; not treatment-related)] | |
| Doss et al. [80] | Multicenter, randomized, DB, phase 4 study | Mod-sev facial AD (Rajka and Langeland score of 4.5–9; facial BSA ≥ 10%), ≥ 16 years, N = 568 | 1:1 TAC, 0.1% vs. fluticasone ointment, 0.005% (facial lesions), or OL fluticasone ointment, 0.005% (all other lesions) BID for up to 3 weeks, followed by a second 3-week period of no study treatment, QD study treatment, or BID treatment with the other drug | Burning sensation — 16.0% (TAC, n = 46, face), 0.3% (TAC, n = 1, nonfacial), 2.9% (fluticasone, n = 8, face), 0.4% (fluticasone, n = 1, nonfacial) | Pruritus — 3.1% (TAC, n = 9, face), 1.0% (TAC, n = 3, nonfacial), 2.2% (fluticasone, n = 6, face), 1.1% (fluticasone, n = 3, nonfacial) | Most AEs in both groups were ASRs |
| References   | Study design | Patient characteristics | Treatment and duration | Frequency of application site | Frequency of application site | Frequency of application site |
|--------------|--------------|--------------------------|------------------------|-------------------------------|-----------------------------|-------------------------------|
| Doss et al.  | Multicenter, DB, randomized, noninferiority study | Mod-sev AD unresponsive to TCS (Rajka and Langeland A severity criteria are detailed in [88]) | 1:1 TAC, 0.03% vs. fluticasone ointment, 0.005% BID for up to 3 weeks to all lesions except eyelids, with optional additional 3 weeks QD treatment | Burning sensation\(^a\)—7.6% (TAC, \(n = 18\)), 2.5% (fluticasone, \(n = 6\)) | Pruritus\(^d,e\)—4.2% (TAC, \(n = 10\)), 3.3% (fluticasone, \(n = 8\)) | AS AEs (unspecified)—days 1–21: 18.0% (TAC, \(n = 43\))\(^b\), 11.3% (fluticasone, \(n = 27\)); days 21–42: 4.1% (TAC, \(n = 9\)), 1.3% (fluticasone, \(n = 3\)) |
| Rahman et al. | Randomized controlled trial | AD \(\text{mean EASI at baseline } 11.29\) (TAC), 11.05 (HA), 2–10 years, \(N = 479\) | 1:1 TAC, 0.03% vs. HA ointment, 1% BID for 3 weeks treatment | Burning sensation\(^d\)—23.3% (TAC, \(n = 7\)), 3.3% (HA, \(n = 1\)) | Localized pruritus—10.0% (TAC, \(n = 3\)), 3.3% (HA, \(n = 1\)) |

\(AD\) atopic dermatitis, \(AE\) adverse event, \(AS\) application site, \(ASR\) application site reaction, \(BID\) twice daily, \(BSA\) body surface area, \(DB\) double blind, \(EASI\) Eczema Area and Severity Index, \(HA\) hydrocortisone acetate, \(HCB\) hydrocortisone butyrate, \(IGA\) Investigator’s Global Assessment, \(Mi\) mild, \(Mo\) moderate, \(MPA\) methylprednisolone aceponate, \(OL\) open label, \(PIM\) pimecrolimus cream, \(QD\) once daily, \(Sev\) severe, \(TA\) triamcinolone acetonide, \(TAC\) tacrolimus ointment, \(VEH\) vehicle

\(^{a}\) Rajka and Langeland AD severity criteria are detailed in [88]

\(^{b}\) Significant difference from vehicle or other treatment category in frequency

\(^{c}\) Among most common treatment-related TEAEs or application site reactions

\(^{d}\) Not specified if application site event

\(^{e}\) Among most common TEAEs
| References          | Study design                        | Patient characteristics | Treatment and duration | Frequency of application site burning, stinging, pain, discomfort | Frequency of application site pruritus, erythema | Frequency of application site paresthesia, other |
|---------------------|-------------------------------------|-------------------------|------------------------|---------------------------------------------------------------|------------------------------------------------|--------------------------------------------------|
| Paller et al.       | Two phase 3, multicenter, randomized, vehicle-controlled, DB studies | Mi-mod AD (ISGA score of 2 or 3; ≥ 5% treatable BSA), 2–79 years, N = 1522 | 2:1 Crisaborole ointment, 2% vs. vehicle BID to all affected areas except the scalp for 28 days | Pain (burning/stinging)\(^{a,b}\) — 4.4% (crisaborole, n = 45)\(^{c}\), 1.2% (VEH, n = 6) | Pruritus— 0.5% (crisaborole, n = 5), 1.2% (VEH, n = 6) |                                                  |
| Eichenfield et al.  | Multicenter, OL extension of phase 3 studies | Mi-mod AD (ISGA score of 2 or 3), 2–72 years, N = 517 | Crisaborole ointment, 2% BID to all affected areas except the scalp for up to 52 weeks | Pain\(^a\) — 2.3% (n = 12), 6 pain events (1.2%) occurred during 48-week long-term extension |                                                  |                                                  |

\(AD\) atopic dermatitis, \(AE\) adverse event, \(BID\) twice daily, \(BSA\) body surface area, \(DB\) double blind, \(ISGA\) Investigator’s Static Global Assessment, \(Mi\) mild, \(Mo\) moderate, \(OL\) open label, \(QD\) once daily, \(Sev\) severe, \(VEH\) vehicle

\(^{a}\) Among most common treatment-related TEAEs or application site reactions

\(^{b}\) Considered treatment-related or possibly treatment-related

\(^{c}\) Significant difference from vehicle in frequency
Cyclooxygenase and downstream prostaglandin synthesis and inhibition of the TRPV1 heat/pain receptor [86], which is activated following exposure to tacrolimus in an in vitro porcine model [87].

CONCLUSIONS

Baseline skin pain is common in AD patients, and application of topical therapies can result in AS tolerability issues. In this review of studies evaluating AS reactions to prescription topical therapies, AS tolerability issues, including burning, stinging, and pruritus, occurred at highest frequency in TCIs, followed by crisaborole and TCSs. Comparing these findings merits caution because of differences in study design that complicate direct comparisons of tolerability. Prevalence rates of AS tolerability issues ranged broadly for individual drug classes, and rates in head-to-head comparisons were often quite different than those in studies investigating a single drug class, a pattern that was especially evident for TCSs. Studies included in this analysis often did not provide detailed information about AS specificity, severity, duration, and direct relation to treatment of tolerability issues. There are no completed head-to-head studies comparing crisaborole with TCIs or TCSs; therefore, informed comparisons of AS tolerability cannot be made. Useful strategies for mitigating AS tolerability issues include patient counseling to anticipate AS tolerability issues and regular use of emollients. Further research is needed to understand mechanisms of AS reactions and patient baseline pain/sensitivity. This mechanistic research may inform formulations with improved tolerability or more efficient, personalized selection of topical products best suited to a patient’s skin sensitivity and AD severity.

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