Topical Therapy for Atopic Dermatitis

What is New and the New Paradigm

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KEYWORDS

• Atopic dermatitis • Topicals • Ruxolitinib • Roflumilast • Crisaborole • Tapinarof

KEY POINTS

- Ruxolitinib 1.5% cream is a topical Janus kinase 1 (JAK1)/JAK2 inhibitor approved for mild-to-moderate atopic dermatitis (AD) in patients aged 12+ years. Efficacy data show superiority to triamcinolone 0.1% cream and good disease control up to 1 year.
- Roflumilast cream emerges as a novel and effective daily topical PDE-4 inhibitor for AD, presenting a promising treatment option that has demonstrated significant symptom relief and safety profile.
- Once-daily application of crisaborole, 2% ointment could be a potential long-term maintenance treatment option in children and adult patients with mild-to-moderate AD.
- Topical tapinarof is an aryl hydrocarbon receptor agonist currently under investigation for the treatment of AD, and data thus far demonstrate its efficacy and safety.
- New nonsteroidal topical agents expand our armamentarium in achieving effective long-term disease control in AD, filling a previously unmet need for therapies that balance efficacy with limited long-term adverse effects.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease with the prevalence of 11.3% to 12.7% in children and 6.9% to 7.6% in adults in the United States.[1] It is characterized by a T-helper type 2 (Th2) immune response with upregulation of proinflammatory cytokines including interleukin (IL)-4, IL-5, IL-13, IL-31, and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway.[2] Also central to the pathogenesis of AD is dysfunction of the skin barrier characterized by lower expression of epidermal protein-coding genes such as filaggrin (FLG) and loricrin (LOR), alterations in epidermal lipids, and increased epidermal water loss.[3,4]

Among the Food and Drug Administration (FDA)-approved therapies for AD, topical corticosteroids (TCSs) are the most commonly utilized[5]; however, side effects of long-term use including atrophy, striae, rosacea, perioral dermatitis, acne and purpura, and steroid phobia among patients leads to

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medication nonadherence.[6,7] In addition, there are many gaps in research on TCSs including comparative data between TCS and nonsteroidal topical medications, as well as data on utilization of TCSs in flare prevention and cost-efficacy.[5] Topical calcineurin inhibitors (TCIs) have been recommended as a nonsteroidal alternative to TCSs and are FDA-approved for patients aged 2 years and above.[5] As research continues to provide further insight into the pathogenesis of AD, new topical nonsteroidal medications are increasingly being implemented in AD care. This review provides an update on recent safety and efficacy data, including Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI), and itch numerical rating scale score (NRS4), on the novel topical nonsteroidal medications currently approved by the FDA including, ruxolitinib, PDE-4 inhibitors, and tapinarof, which is currently under investigation for the treatment of AD.

RUXOLITINIB

Ruxolitinib 1.5% cream (Opzelura, Incyte, Wilmington, DE) received FDA approval in September 2021 for short-term (up to 8 weeks) and noncontinuous chronic treatment of mild-to-moderate (IGA score of 2 to 3) AD in nonimmunocompromised patients aged 12 years and older.[8] Ruxolitinib works by inhibiting the JAK-STAT, specifically JAK1 and JAK2.[9] The JAK-STAT pathway plays a pivotal role in the pathogenesis of AD as it is responsible for the recruitment of keratinocytes, immune cells, and peripheral sensory neurons thus propagating pruritus and inflammation.[10] All JAK inhibitors (JAKis) carry black box warnings, referential to data of pan-JAKi tofacitinib in patients aged over 50 years, and at least one cardiovascular risk factor (thus quite a different study population from the usually younger and healthier patients with AD is affected). This includes serious infections, mortality, malignancies (eg, lymphoma), major adverse cardiovascular events (MACEs), and thrombosis.[11]

In maximal-use application studies in adolescents and adults with greater than 25% body surface area (BSA) AD involvement, the mean steady-state ruxolitinib plasma concentration was consistently below the half-maximal inhibitory concentration of JAK-mediated myelosuppression.[12] Pharmacokinetic studies in a phase II and phase III 3 double-blind, vehicle-controlled studies in patients with AD showed that the application of topical 1.5% cream to up to 20% BSA and 60 g per week is not expected to lead to systemic plasma concentrations associated with adverse effects that may be commonly associated with oral JAKis.[13] The most common adverse event (AE) was nasopharyngitis, which, despite not occurring in most patients, was higher in the ruxolitinib compared to the placebo group.

Phase III, randomized, double-blinded studies (TRuE-AD) have shown how topical ruxolitinib achieved the primary endpoint of an IGA score of 0 to 1 and 2 or greater grade improvement from baseline at week 8 compared with placebo. There have only been a limited number of studies comparing the newer nonsteroid anti-inflammatory agents to topical steroids. However, the Phase II trial (TRuE-AD1) compared twice daily application of topical ruxolitinib to triamcinolone cream 0.1%. After 4 weeks, ruxolitinib showed superiority in several endpoints compared to triamcinolone including IGA clear/almost clear (38% vs 25.5%), EASI-75 (56% vs 47.1%), EASI-90 (26% vs 14.7%) and NRS4-point itch reduction (62.5% vs 32.3%). Impressively, itch relief occurred as fast as 2 days after the first application.[14,15]

Topical ruxolitinib also showed good disease control in open extension studies up to 1 year with an IGA score of 0 or 1 in 74% to 78% of patients at week 52 and 1% to 2% BSA,[16] a dataset that was not available at the time of the American Academy of Dermatology (AAD) guidelines for topical therapy in adults.[5] A recent study (TRUE AD-3) aimed to assess the safety, pharmacokinetics, and efficacy of 0.75% to 1.5% ruxolitinib cream in children and adolescents (2–<12 years) with AD. After twice-daily application for 28 days, ruxolitinib cream showed no serious treatment-emergent AEs. Additionally, no effect on blood counts or bone biomarkers were observed.[17] The study met its primary endpoint and showed significantly more patients treated with ruxolitinib cream 0.75% and 1.5% achieved IGA 0 (clear) or 1 (almost clear) with at least a 2 point improvement from baseline at week 8, compared to vehicles. Safety data was consistent with what was observed in adults, with low rates of discontinuation.[18]

PDE-4 INHIBITORS

PDE-4 is an intracellular enzyme mainly present in immune, epithelial, and brain cells that regulates inflammation and epithelial integrity by degrading cyclic adenosine monophosphate.[19] PDE-4 inhibition mediates inflammatory cytokines and has been utilized in various forms for respiratory diseases, cutaneous psoriasis, psoriatic arthritis, and AD.[20,21]

Roflumilast

Topical roflumilast, is a novel PDE-4 inhibitor that has shown efficacy in managing psoriasis, AD, and seborrheic dermatitis, with respective formulations tailored to each condition.[22–24] Specifically,

the 0.3% cream formulation is FDA-approved for psoriasis treatment in patients aged 6 years and older, while the 0.3% foam is sanctioned for those aged 9 years and above with seborrheic dermatitis. In the development program for AD, roflumilast 0.15% cream has successfully demonstrated its therapeutic potential in 2 phase III trials (INTEGUMENT-1: NCT04773587[25] and INTEGUMENT-2: NCT04773600[26]). In the clinical studies, patient eligibility was determined by being aged 6 years or older, having a validated investigator global assessment (vIGA)-AD score of 2 or 3, a BSA involvement of 3 or more, and an EASI score of 5 or greater. Significantly higher percentage (31.3%) of patients achieved vIGA-AD success, defined as "Clear" or "Almost Clear" skin plus a 2 grade improvement from baseline. Roflumilast cream significantly reduced EASI scores, with 377 out of 884 patients (42.7%) of patients achieving 75% reductions in EASI scores by the end of the study period. Improvements in itch were noted as early as 24 hours after the first application of roflumilast cream, and these improvements were more significant than those observed with the vehicle. Roflumilast cream was well tolerated with low incidence of application site AEs. Tolerability was high, with most participants reporting minimal to no discomfort at the application site.

These findings are corroborated by another phase III trial of 0.05% roflumilast cream (INTEGUMENT-PED: NCT04845620)[27] that displayed roflumilast's effectiveness and safety in a pediatric cohort aged 2 to 5 years. The study demonstrated that roflumilast was well tolerated and effective, showing significant improvements in AD symptoms over 4 weeks. Marked improvement in vIGA-AD scores with significant differences from the vehicle were recorded, appearing as early as week 1. A total of 154 out of 436 patients (35.3%) achieved a vIGA-AD status of clear or almost clear at week 4. Additionally, 172 out of 436 patients (39.4%) reached EASI-75. Pruritus, assessed daily, also showed significant improvements from baseline, which were noticeable within 24 hours after the first application of the cream. The treatment was generally safe with low incidence of AEs, none of which were serious or led to discontinuation in more than a few cases. This aligns with the known safety profile of roflumilast in previous studies on different age groups and conditions. The study's results are promising, suggesting that roflumilast cream 0.05% could be a valuable nonsteroidal treatment option for young children aged 2 to 5 years with AD.

Longer term studies of roflumilast are currently underway to further evaluate its sustained efficacy and safety.

Crisaborole

Crisaborole, 2% ointment, is a PDE-4 inhibitor that has been approved by the FDA for the treatment of mild-to-moderate AD in patients aged as young as 3 months.[28,29]

Recently, the CrisADe CONTROL study investigated the long-term efficacy and safety of crisaborole 2% ointment, as a maintenance treatment of AD (NCT04040192).[30] This study evaluated how effective and safe long-term treatment with once daily crisaborole was compared with a vehicle. Patients who showed high levels of improvement with twice-daily crisaborole during an 8 week run-in period (clear/almost clear [0–1 with a $\geq$2 grade improvement in IGA] and $\geq$50% EASI improvement) were randomized to receive either crisaborole or vehicle once daily for 52 weeks. The study included 497 patients initially, with 270 successfully completing the run-in period and being randomized for the maintenance phase. The median time to the first flare was significantly longer for patients treated with crisaborole (111 days) compared to those receiving the vehicle (30 days). Patients treated with crisaborole experienced more flare-free days on average (234 days) than those treated with the vehicle (199.4 days) and had fewer flares (average of 0.95 flares) compared to those on the vehicle (average of 1.36 flares). Crisaborole was well tolerated with no new or unexpected safety findings reported. These results indicate that once-daily treatment with crisaborole could be a potential long-term maintenance treatment option in children and adults with mild-to-moderate AD.

TAPINAROF

Topical tapinarof 1% (VTAMA, Dermavant Sciences, Inc., Morrisville, NC) (TAP1%) is an aryl hydrocarbon receptor (AhR) agonist currently approved for the treatment of plaque psoriasis in adults and under investigation for the treatment of AD.[1,2] The AhR is a ligand-activated transcription factor expressed in keratinocytes and a variety of immune cells.[31–33] AhR activity promotes the integrity of the skin barrier and regulates skin homeostasis[31]; it has been shown to upregulate skin barrier components including LOR, involucrin, FLG, hornerin, and ceramide lipids, attenuate the generation and survival of resident memory T cells, and decrease Th2 proinflammatory cytokines including IL-4, IL-5, IL-13, and IL-31.[34–36] A recent study utilizing human immortalized keratinocytes treated with AhR ligands demonstrated Tapinarof's ability to attenuate the expression of multiple IL-13-dependent, AD-related genes including eosinophil chemoattractant CCL26 (eotaxin-3).[37] In addition,

AhR may function through antioxidant activity through nuclear factor erythroid 2-related factor (Nrf2)-mediated pathways.[34,35]

A phase IIa, open-label, maximum-use trial of tapinarof cream among patients aged 2 to 17 years with vIGA for AD score of 3 or greater and 25% or greater BSA involvement (12–17 years) or 35% or greater involvement showed that tapinarof was well tolerated with a consistent pharmacokinetic profile and performance among all ages and disease states, low incidence of AEs with no significant systemic AEs, no contact dermatitis, and minimal to no systemic exposure under maximal use conditions for patients with up to 90% BSA affected.[38] ADORING 1 and 2 were 2 identical recent phase III clinical trials including 407 (ADORING 1) and 406 (ADORING 2) adult and pediatric patients aged 2 years or older with vIGA-AD 3 or greater, 5% to 35% BSA, and EASI 6 or greater. After 8 weeks, these trials demonstrated significant reductions in vIGA (45% TAP1% vs 14% vehicle and 46% TAP1% vs 18% vehicle in ADORING 1 and 2, respectively, achieved vIGA-AD success, defined as vIGA-AD 0 or 1 with 2 point or greater improvement from baseline, both $P < .0001$), EASI 75 (56% TAP1% vs 23% vehicle and 59% TAP1% vs 21% vehicle in ADORING 1 and 2, respectively, both $P < .0001$), and 4 point reduction or greater in PP-NRS (56% TAP1% vs 34% placebo [$P = .0366$] and 53% TAP1% vs 24% vehicle [$P = .0015$] in ADORING 1 and 2, respectively).[39] Safety data demonstrated that AEs were mild to moderate and the discontinuation rate was decreased compared to vehicle (ADORING 1: 1.9% TAP1% vs 3.6% vehicle; ADORING 2: 1.5% VTMA vs 3.0% vehicle).[39]

In addition, tapinarof treatment resulted in meaningful improvements in patient-reported outcomes including dermatology life quality index (DLQI), children's dermatology life quality index (CDLQI), infants' dermatitis quality of life index (IDQOL), and patient-oriented eczema measure (POEM) (Simpson AAD presentation).[40] The most common AEs in phase III trials were "follicular events," observed in approximately 9% to 10% of patients with AD on tapinarof and headache. Interim analysis of ADORING 3, a 48 week open-label, long-term extension study among 711 patients with vIGA-AD 3 or greater, demonstrated safety of tapinarof and continued improvements in efficacy beyond 8 weeks (Adoring 3 press release).[39,41]

PARADIGM: NOVEL AND TRADITIONAL TOPICALS IN REGIMENS OF CARE

Topical anti-inflammatories remain a mainstay in the management of pediatric AD. Best practices in prescribing topical agents include delineation of both flare and maintenance regimens and adequate explanation of appropriate volumes to use for each scenario. Especially in the pediatric population, fear of side effects of topical agents, especially topical steroids, as well as a lack of understanding of appropriate volumes to apply for different body sizes and disease extent can contribute to undertreatment and poor adherence. The principle of suggesting appropriate quantities of topical medication to use for varying surface area and body size has been termed "volumetric prescriptions."[42] A standardized tool facilitating volumetric prescriptions was developed in a support program for pediatricians to improve care of AD. This "topical medication volume calculator" is integrated into the electronic health record and estimates the volume (in grams) of topical medications to be used in a typical several-week tapered regimen based on patient age and BSA involvement. This was shown to improve provider management of pediatric AD.[42]

Though in most studies novel topical agents are employed as monotherapy and compared to vehicle as part of the drug approval process, in clinical practice, these therapies will likely be utilized in multiagent regimens of care, which may include traditional emollients, good bathing practices, traditional topical steroids, calcineurin inhibitors, and newer nonsteroid anti-inflammatory agents.

Recent guidelines from prominent US and international groups (eg, American Academy of Dermatology, Consensus-based European Guidelines, and American Academy of Allergy, Asthma and Immunology) vary in recommendations for the use of topical therapies for AD and are without specific algorithms for the use of different agents in regimens of care. Commonalties among most of the guidelines are the use of moisturizers as a core aspect of treatment, recognition of topical steroids of varying strengths as a mainstay of therapy, and the use of nonsteroid prescription agents as an alternative to TCS for AD that is refractory to moisturizers, either as reactive therapy for signs and/or symptoms of AD, or as proactive therapy. Factors that can influence selection of topical agents include disease severity, extent, regional anatomy, response to prior therapies, disease course, tolerance to medications, patient and caregiver preference, as well as cost and access.

We propose that providers establish an expectation of long-term disease control, striving for minimal signs of AD, minimal itch, and minimal sleep disturbance. A standard paradigm should be initiation of therapeutic regimens stressing "good skin care" with culturally-accepted bathing and moisturization

practices and use of TCSs generally as first-line anti-inflammatory agents for AD unresponsive to general measures, with TCIs (pimecrolimus and tacrolimus), PDE-4 inhibitors (crisaborole and roflumilast), topical JAKis (ruxolitinib), or tapinarof as alternative agents to be considered, subject to drug approval, age or BSA restrictions, as well as cost and access considerations. Beyond acute disease control, intermittent use of TCS or the above nonsteroid agents may be used either "as needed," or in proactive regimens. A recent European study aimed to compare the effects of proactive treatment with tacrolimus ointment and mometasone furoate on the epidermal barrier structure and ceramide levels of patients with AD, showed superiority of TCI.[43]

While there is burden associated with topical regimens for patients and families in terms of time spent applying medicines, cost, and side effects, regimens incorporating new nonsteroidal agents (the PDE-4 inhibitors crisaborole or roflumilast, aryl-hydrocarbon receptor agonist tapinarof, and topical JAKi ruxolitinib) along with TCIs present a paradigm shift in terms of high efficacy in improving inflammation, itch, and barrier function, while limiting the adverse effects associated with long-term use of TCSs. The newer nonsteroid agents expand our armamentarium to achieve effective long-term disease control in AD, either with regimens of care relying on topical medications or together with systemic agents.

CLINICS CARE POINTS

- Evolving non-steroidal topical agents for atopic dermatitis include JAK-inhibitors, PDE-4 inhibitors and an aryl hydrocarbon receptor agonist, all of which can be useful as anti-inflammatory agents.
- Topical ruxolitinib has been studied utilizing a maximum application useage recommendation of no more than 20% body surface area application.
- "Volumetric presribing," setting expectations of volume of application of a topical agent to use over a period of time, may improve outcomes of AD care.

DISCLOSURE

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