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LEADING ARTICLE

Topical Management of Pediatric Psoriasis: A Review of New Developments and Existing Therapies

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Abstract

Psoriasis is a chronic immune-mediated disorder that commonly affects adults and children. In recent years, pediatric psoriasis has increased in prevalence and the disease is often associated with various comorbidities and psychological distress. The conventional topical treatments for psoriasis, such as corticosteroids, calcineurin inhibitors, vitamin D analogs, anthralin, and coal tar, are often limited by their side effects, tolerability, and/or efficacy, particularly for use in children and on sensitive and intertriginous areas. Recently, the US Food and Drug Administration approved two new topical non-steroidal agents for treating psoriasis that target different pathogenic pathways than the conventional treatments. Roflumilast is a phosphodiesterase type 4 inhibitor approved for the treatment of plaque psoriasis in patients aged 12 years and older. Tapinarof is a novel aryl hydrocarbon receptor modulator approved for adult psoriasis and currently undergoing studies for pediatric psoriasis. Ongoing efforts are also being made to optimize conventional treatments, for instance, a new foam formulation of halobetasol propionate was recently approved for pediatric psoriasis. Clinical trials of various new drugs targeting one or multiple pathogenic pathways of psoriasis, such as Janus kinase inhibitors, different formulations of phosphodiesterase type 4 inhibitors, and aryl hydrocarbon receptor modulators have also been explored. The recent emergence of novel topical agents provides promising new options for managing pediatric psoriasis with the potential to improve clinical outcomes and quality of life. In this article, we review the mechanism of action, efficacy, and safety profile of novel topical agents and discuss their potential roles in the management of pediatric psoriasis.

1 Introduction

Psoriasis is a common chronic immune-mediated disorder affecting 1–3% of the general population [1, 2]. The prevalence of psoriasis in the pediatric population has increased, and one third of all patients develop symptoms in childhood and adolescence [1–3]. Pediatric psoriasis, like its adult counterpart, is associated with various co-morbidities, including metabolic syndromes (obesity, hyperlipidemia, hypertension, insulin resistance, and diabetes mellitus), psoriatic arthritis, and cardiovascular disease [2–4]. Pediatric psoriasis also causes psychological distress, leading to a higher risk of depression, anxiety, and bipolar disorder [5, 6]. Recently, based on a better understanding of the pathophysiology of psoriasis, novel topical and systemic agents have increased in number. Compared with adults with psoriasis, children and adolescents are more likely to experience milder focal disease and involvement of facial and anogenital areas [4, 7]. Facial and anogenital skin are sensitive and more susceptible to the side effects caused by topical agents. Parental concern over the use of topical corticosteroids in their children is also an important consideration as it can interfere with the adherence and effective use of topical therapies. These concerns highlight the need for more topical options, in particular those that have less side effects than existing topical corticosteroids, and with better tolerability and higher efficacy than conventional topical non-steroidal agents. In recent years, several new topical agents for managing pediatric psoriasis have emerged,

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Key Points

Pediatric psoriasis is common and increasing in prevalence. The proportions of mild cases and diseases involving facial and anogenital areas are higher in the pediatric population, highlighting the need for effective, safer, and more tolerable topical therapies.

The US Food and Drug Administration recently approved two new non-steroidal topical agents for psoriasis.

Roflumilast is a phosphodiesterase type 4 inhibitor approved for the treatment of plaque psoriasis in patients aged 12 years and older. Tapinarof is a novel aryl hydrocarbon receptor modulator approved for adult psoriasis and currently undergoing studies for use in pediatric psoriasis.

There are ongoing efforts to optimize existing topical therapies. A foam formulation of halobetasol propionate with fewer side effects was recently approved for treating psoriasis in patients aged 12 years and older.

Emerging new topical agents provide promising new options for managing pediatric psoriasis with the potential to improve clinical outcomes and quality of life.

bridging the gap in innovation in this area since the approval of calcipotriene in the 1990s. In this article, we review the mechanisms of action and the efficacy and safety profiles of recently approved topical agents, examine therapeutic targets in the pipeline, and discuss the potential roles of these new additions in the topical management of pediatric psoriasis.

2 Established Topical Treatments

2.1 Topical Agents for Pediatric Psoriasis

Topical corticosteroids (TCS) are a well-established and effective therapy for psoriasis in children and adults. In children, particularly those aged younger than 12 years, systemic absorption of TCS leading to hypothalamic-pituitary-adrenal (HPA) axis suppression should be considered [8]. Additionally, the side effects of skin atrophy, dyspigmentation, and telangiectasia often limit the location, frequency, and duration of the use of TCS. Usage on sensitive areas such as periocular skin can sometimes lead to unintended ocular side effects, such as glaucoma and cataracts. Furthermore, parental concern over the use of TCS is also an important consideration that can impede the adherence and effective use of TCS. For these reasons, it is not a preferred first-line therapy for face, genitalia, and intertriginous areas. For these areas, topical calcineurin inhibitors (TCIs), such as pimecrolimus and tacrolimus, have better adverse effect profiles and are the preferred first-line options, although burning, stinging, pruritus, and irritation often limit their use in pediatric patients [2, 9, 10]. Notably, TCIs are currently not approved by the US Food and Drug Administration (FDA) to treat psoriasis, thus insurance denial may be a common barrier to accessing this therapeutic option [11, 12].

Topical vitamin D analog (such as calcipotriene, calcitriol, and calcipotriol), while often not as effective as high-potency TCS, can be an efficacious and safe therapy. Therefore, it is recommended as a first-line monotherapeutic option for pediatric psoriasis [10, 13]. In practice, however, local irritation makes it less tolerated when used on the face, genitals, and intertriginous skin. Additionally, there is a theoretical risk of hypercalcemia and hypovitaminosis D from systemic absorption, particularly in younger children or in those with large affected areas [2]. An 8-week phase IV study showed no adverse events (AEs) related to calcium metabolism when calcitriol 3-mcg/g ointment was applied twice daily in patients aged 2–12 years with mild-to-moderate psoriasis [14]. However, the use of topical vitamin D preparations should still be done with great caution, or avoided if necessary, particularly in patients with demonstrated hypercalcemia or renal disease.

Anthralin is a treatment option for managing pediatric psoriasis either as a scalp solution or with daily applications of 0.01–4% formulations for 15–45 min. Irritation is a common adverse effect, in addition to burning, stinging, pruritus, and erythema. Anthralin can temporarily stain the skin, and permanently stain clothing, shower, and appliances. The aforementioned AEs of anthralin limit its use [2], and it may be difficult to obtain these products.

Topical coal tar combined with narrow-band ultraviolet phototherapy (Goeckerman treatment) is historically an effective therapy for psoriasis [15], but uncommon in clinical practice. The exact mechanism of action is unclear. Prolonged use, however, carries a risk of carcinogenicity and studies have shown urinary excretion of coal tar metabolites and chromosomal aberrations of lymphocytes in children with psoriasis treated with the Goeckerman formulation [16, 17]. Other AEs limiting its use include irritation, folliculitis, contact dermatitis, and phototoxicity. Similar to anthralin, it may stain the skin, clothing, shower, and appliances. Coal tar as a monotherapy for pediatric psoriasis has not been formally studied either. Given these considerations, Goeckerman treatment has become less popular and rarely used in pediatric patients.

Combination topical therapy is commonly employed to achieve superior efficacy while mitigating the side effects of

each component. Calcipotriol with betamethasone dipropionate (ointment and suspension) is FDA approved to treat body and scalp psoriasis in patients aged 12 years and older. A 4-week phase II study showed no clinically significant dysregulation of the HPA axis nor calcium homeostasis with once-daily application on the body and scalp for patients with psoriasis aged 12–16 years [13]. In adults, this formulation was shown to be more effective than using calcipotriol alone [18]. While effective, combination therapy with high-potency TCS should still be used cautiously given its known side effects. Another combination treatment utilizes 6–10% salicylic acid for 1 week prior to calcipotriene monotherapy. This may enhance the efficacy of calcipotriene, but notably, the acidity of salicylic acid can inactivate calcipotriene when used simultaneously [2, 19].

2.2 Topical Agents Approved for Adult Psoriasis

Tazarotene is a topical retinoid that is FDA approved in 0.05% and 0.1% gel formulations for treating plaque psoriasis in adults [2]. The literature on its use in pediatric patients is limited to case reports, such as use for nail psoriasis in a 6-year-old child who improved after 8 weeks of once-daily use of a tazarotene 0.05% gel with local irritation as a side effect [20]. Similar to other non-steroidal agents, common side effects of tazarotene include burning, pruritus, and erythema. Akin to combining calcipotriol and betamethasone, combining tazarotene with TCS provides synergistic efficacy while minimizing the side effects of both, including non-steroid-related irritation and steroid-related atrophy. A particular lotion formulation of tazarotene 0.045% with halobetasol propionate 0.01% is a preparation that is effective and showed a maintenance of effect for at least 1 month after stopping topical application. An open-label phase IV study is ongoing to evaluate its safety and systemic exposure including its impact on the HPA axis in patients aged 4–17 years with moderate-to-severe plaque psoriasis [21, 22]. Notably, tazarotene is teratogenic and contraindicated in pregnancy, and this should be considered in female adolescents of childbearing potential.

Salicylic acid is also used for its keratolytic properties to treat psoriasis in adults. Salicylic acid 5–10% can be used as monotherapy or combined with other topical agents, including TCS, TCIs, and calcipotriene [2, 23]. Studies have shown greater efficacy of mometasone furoate 0.1% when combined with salicylic acid 5% for moderate-to-severe plaque psoriasis, and tacrolimus ointment was also more effective when used with salicylic acid 6% gel [24, 25]. The synergistic effect is likely due to increased penetration of the drug from the keratolytic property of salicylic acid.

3 Newly Approved Topical Agents for Pediatric Psoriasis

3.1 Roflumilast

In July 2022, the FDA approved the use of roflumilast 0.3% cream, a phosphodiesterase type 4 (PDE-4) inhibitor, in once-daily application for the treatment of plaque psoriasis in patients aged 12 years and older [26]. Phosphodiesterase type 4 is an intracellular enzyme with a known proinflammatory effect in psoriatic skin. The inhibition of PDE-4 promotes protein kinase A activation via cyclic adenosine monophosphate, which leads to downstream upregulation of anti-inflammatory cytokines and downregulation of pro-inflammatory cytokines involved in psoriasis pathogenesis, such as tumor necrosis factor-α, interferon-γ, interleukin (IL)-2, IL-12, IL-17, and IL-23 [27, 28].

Most recently, twin 8-week phase III studies (DERMIS-1 and DERMIS-2) demonstrated the efficacy and safety of roflumilast 0.3% cream in patients aged 2 years and older with plaque psoriasis, including its use for intertriginous areas [29]. At week 8, 37.5–42.4% of roflumilast-treated patients achieved Investigator's Global Assessment (IGA) success (clear/almost clear with a ≥ 2 grade improvement) compared with 6.1–6.9% of vehicle-treated patients ($P < 0.001$). Furthermore, 39.0–41.6% of roflumilast-treated patients had a 75% reduction in their Psoriasis Area and Severity Index score compared with 5.3–7.6% of vehicle-treated patients ($P < 0.001$). Clinical management of intertriginous areas are often limited by thinner skin, a higher friction area, and greater drug absorption, which leads to a higher susceptibility for irritation and side effects of conventional topical therapies [30]. In this regard, roflumilast exhibited efficacy in the intertriginous areas: 68.1–71.2% achieved intertriginous IGA success compared with 13.8–18.5% of the vehicle arm ($P < 0.001$). Moreover, pediatric patients with psoriasis often experience pruritus. Roflumilast showed superior efficacy against itch: 67.5–69.4% of participants in the treatment group had a ≥ 4-point reduction in their Worst Itch Numeric Rating Scale score compared with 26.8–35.6% in the control group ($P < 0.001$) [20, 21], adding to its known beneficial effect on itch-related sleep loss and Dermatology Life Quality Index scores [31]. Roflumilast also decreased the impact of psoriasis on a patient's life: − 49.3 to − 50.1 change in the Psoriasis Symptom Diary score was seen in the treatment group compared with − 19.2 to − 22.8 in the control group ($P < 0.001$). The AE profile was similar between the roflumilast and vehicle groups, with no relevant serious AEs. Few reports of stinging, burning, and application-site reactions were found in both arms. Furthermore, systemic absorption of topical roflumilast appears negligible as its bioavailability is less than 2% [32]. The most common AEs

were diarrhea and headache (< 4%). Overall, roflumilast 0.3% cream was very well tolerated with a < 2% rate of study discontinuation [28].

Two open-label, 4-week, phase II studies (for children aged 2–5 years and children aged 6–11 years) and one open-label, 2-week, phase I study for 12 years and older (MUSE) are underway to investigate the maximum use pharmacokinetics and safety of roflumilast 0.3% cream in patients with psoriasis aged 2 years and older (NCT04746911, NCT04655313, NCT04279119). Another open-label, 24-week, phase III study (DERMIS-OLE) is also underway to examine its long-term safety (NCT04286607).

In addition to the cream formulation, an 8-week phase II study demonstrated the safety and efficacy of a once-daily application of roflumilast 0.3% foam formulation to treat scalp and body psoriasis in patients aged 12 years and older [33]. At week 8, 59.1% of participants achieved scalp IGA success compared with 11.4% of vehicle-treated patients ($P < 0.001$). Secondarily, 40.3% achieved body IGA success compared with 6.8% of the control arm. 67.2% of roflumilast-treated patients had a 75% reduction in the Psoriasis Scalp Severity Index score compared with 21.8% of vehicle-treated patients ($P < 0.001$) and 46.7% compared with 3.4% showed a 90% reduction in the Psoriasis Scalp Severity Index score ($P < 0.001$). This formulation is also effective against itch: 71.0% of the treatment group had a ≥ 4-point reduction in their Scalp Itch Numeric Rating Scale score compared with 18.5% in the control group ($P < 0.001$). Roflumilast 0.3% foam surpassed the vehicle in terms of improving the impact of disease with a − 55.0 change in the Psoriasis Symptom Diary score compared with − 27.5 in the control group ($P < 0.001$). Among the 304 study participants, the only AE reported was a testicular torsion in one patient receiving roflumilast. An 8-week phase III study (ARRECTOR) investigating the efficacy and safety of a once-daily application of roflumilast 0.3% foam for treating scalp and body psoriasis in patients aged 12 years and older is currently ongoing (NCT05028582).

Inhibiting PDE-4 has been known to improve psoriasis flares. Apremilast, the only oral PDE-4 inhibitor in the market, shows moderate efficacy in treating plaque psoriasis, but may be limited mainly by its gastrointestinal side effects [34]. Pharmacokinetic studies showed that topical application of roflumilast over 28 days exhibited a higher concentration found in the skin than in the blood, suggesting local PDE-4 inhibition occurring primarily in the skin [32]. Crisaborole is an existing topical PDE-4 inhibitor in the market approved for atopic dermatitis. It has not received an indication for psoriasis, but successful off-label use has been reported [35, 36]. Frequent local irritation and burning sensation unfortunately have substantially limited its use. Roflumilast, in contrast, has a greater affinity for PDE-4 than crisaborole and apremilast, and is 50–300 times more potent [27, 37]. Unlike its predecessors, roflumilast shows minimal stinging, burning, pain, or application-site reactions in studies to date, suggesting a much better tolerability compared with crisaborole, and as a topical medication with minimal bioavailability, it has very limited, if any, gastrointestinal side effects with which apremilast is associated [29]. In addition to good safety and tolerability, roflumilast enriches the armamentarium of psoriasis therapy within this class.

3.2 Halobetasol Propionate 0.05% Foam

Although multiple pathways are known to be involved in the pathogenesis of psoriasis and novel therapeutic targets are emerging, TCS are still the first choice in the treatment of psoriasis. Recently, a foam formulation was developed that reduces systemic absorption, is more convenient for applying over large body surface areas, and may have a decreased "greasy feel" than ointments or other cream formulations [38].

Halobetasol propionate is a super-high potency corticosteroid and has been used for plaque psoriasis only in adults. However, with the advent of the foam formulation, halobetasol propionate 0.05% foam received FDA approval in 2021 for treating psoriasis in adolescents aged 12 years and older [38]. Two double-blind, randomized, 15-day phase III studies with twice-daily applications were conducted in adults with moderate-to-severe psoriasis (NCT03988439). Both studies revealed IGA success (clear/almost clear with a ≥ 2 grade improvement) of 25.3–30.7% versus 3.9–7.4% in the placebo group. Adverse skin reactions are similar to former TCS, including local burning sensation, skin atrophy, telangiectasia, and folliculitis.

Pediatric patients have a higher systemic absorption rate of topical agents than adults, thus systemic side effects such as adrenal suppression must be considered. The safety of a twice-daily application of halobetasol propionate 0.05% foam for patients aged 12–17 years was evaluated in an open-label, 2-week, phase IV study [39]. On day 15, 26.1% of patients showed HPA-axis suppression, but none reported any clinical symptoms and all returned to normal adrenal function 4 weeks after the discontinuation of halobetasol. In summary, up to 2 weeks of a twice-daily application of halobetasol propionate 0.05% foam is effective and safe in patients with psoriasis aged 12 years and older.

4 Potential Topical Agents for Pediatric Psoriasis

4.1 Aryl Hydrocarbon Receptor Modulator

4.1.1 Tapinarof

Tapinarof is a novel topical aryl hydrocarbon receptor (AhR) modulator initially developed for the treatment of atopic dermatitis. Recently, the FDA approved the once-daily application of the 1% cream formulation for the treatment of adult psoriasis [28, 40–42]. While yet to receive FDA approval to treat psoriasis in children, a phase III study is currently underway studying its use for pediatric psoriasis (NCT05172726).

Aryl hydrocarbon receptor is a ligand-dependent transcriptional factor that regulates the terminal differentiation of T-helper 17 and T-helper 22 cells [43, 44]. Tapinarof binds to AhR to downregulate proinflammatory cytokines, including IL-17A, IL-17F, and IL-22 [45]. Furthermore, tapinarof is an intrinsic antioxidant that can induce the expression of antioxidant enzymes via the AhR-nuclear factor erythroid 2-related factor pathway [45]. These effects of tapinarof reduce epidermal oxidative stress. In addition, AhR signaling regulates skin-barrier protein expression in the keratinocyte differentiation pathway including fillagrin, loricrin, and involucrin, which is the mechanism that supports the use of tapinarof in atopic dermatitis in addition to psoriasis [45].

Two phase III studies (PSOARING 1 and 2) and an open-label trial (PSOARING 3) in adult patients with mild-to-severe plaque psoriasis have been reported [41, 42]. The PSOARING 1 and 2 were 12-week, randomized, double-blind, vehicle-controlled trials evaluating the efficacy and safety of tapinarof 1% cream in adult patients with plaque psoriasis. 35.4–40.2% of the tapinarof-treated group achieved Physician's Global Assessment success (clear/almost clear with a ≥ 2 grade improvement) compared with 6.0–6.3% of vehicle-treated patients ($P < 0.001$). Tapinarof showed good tolerability when used in sensitive and intertriginous skin, as evidenced by a low rate of burning and stinging sensation [41, 42].

Tapinarof also showed favorable safety and side effect profiles. Although AEs occurred in 50.3–54.5% of the tapinarof group, versus 22.4–26.2% in the placebo group, there were no serious AEs related to tapinarof and treatment discontinuation related to AEs was rare. The most frequent AE was mild folliculitis that occurred several weeks after initiating treatment, reported by 17.8–23.5% of participants in the tapinarof group versus 0.6–1.2% of the vehicle group. The mechanism by which folliculitis occurs is not yet clear, but as tapinarof is involved in the expression of skin barrier proteins, it may be associated with plugging of hair follicles through overexpression of proteins in the stratum corneum [40]. Nasopharyngitis and headache have also been reported. Given the low systemic absorption of tapinarof, the mechanism for the low level of AEs is not clear at this time [40].

Recently, the PSOARING 3 study evaluating the 1-year safety and efficacy of tapinarof cream for plaque psoriasis revealed a high rate of complete clearance (40.9%), Physician's Global Assessment success of 58.2%, no tachyphylaxis, and efficacy maintenance after discontinuing therapy up to 4 months [42]. Furthermore, the satisfaction level (in terms of effectiveness, ease of use, and cosmetic elegance) of prolonged use of tapinarof 1% cream up to 40 weeks was higher than that of prior topical treatments [46], which may improve treatment adherence and effectiveness.

Studies in pediatric patients have not yet been published, but an open-label, multi-center, phase III study for pediatric psoriasis is currently in progress (NCT05172726). In summary, tapinarof 1% cream is safe, effective, and has a durable efficacy for treating adult psoriasis. In addition, tapinarof 1% cream has undergone extensive studies for atopic dermatitis including children down to 2 years of age. It may be a promising non-steroidal alternative for treating pediatric psoriasis in the near future. Table 1 provides a summary of the new and emerging developments in pediatric topical therapies discussed.

4.1.2 Benvitimod

Benvitimod is another AhR modulator that is currently undergoing a phase IV clinical efficacy and safety study for mild-to-moderate psoriasis in adults [47]. While benvitimod and tapinarof contain the same active component (3,5-dihydroxy-4-isopropyltrans-stilbene), they are two distinct topical agents different in excipients and the frequency of administration, and are currently evaluated in separate clinical trials [48, 55]. A 12-week phase III study comparing the twice-daily application of benvitimod 1% cream with calcipotriol 0.005% ointment and placebo showed that the efficacy of bentivimod is similar to calcipotriol and superior to vehicle. Pruritus, contact dermatitis, and folliculitis were the most commonly reported AEs [47].

4.2 Janus Kinase Inhibitors

Janus kinase (JAK) inhibition has been studied in several inflammatory diseases including psoriasis. The inhibition of JAK signaling blocks downstream T-helper 17 differentiation via the suppression of IL-23 signaling, and proinflammatory cytokines such as IL-6, interferon-γ, and tumor necrosis factor signaling pathways, implicated in psoriasis pathogenesis. [49, 50].

Table 1 Overview of new and emerging topical treatments for pediatric psoriasis

Name	Class of medication	US FDA approval for psoriasis	Efficacy (vs vehicle)	Adverse events
Roflumilast 0.3% cream	PDE-4 inhibitor	Age ≥ 12 years	**DERMIS 1 and 2 (phase III)** ≥ 2 years, QD, 8 weeks IGA response: 37.5% vs 6.1%, 42.4% vs 6.9% I-IGA response: 68.1% vs 13.8%, 71.2% vs 18.5% PASI-75: 39.0% vs 5.3%, 41.6% vs 7.6% WI-NRS response: 67.5% vs 26.8%, 69.4% vs 35.6% PSD change: − 49.3 vs − 19.2, − 50.1 vs − 22.8 **PK and safety trials (phases I-II)** Phase II, 2–5 years, QD, 4 weeks Phase II, 6–11 years, QD, 4 weeks Phase I, ≥12 years, QD, 2 weeks (MUSE) Status: in progress (NCT04746911, NCT04655313, NCT04279119) **DERMIS-OLE (phase III)** 2–11 years, QD, 24 weeks Status: in progress (NCT04286607)	Diarrhea, headache, hypertension, nasopharyngitis
Roflumilast 0.3% foam	PDE-4 inhibitor	Age ≥ 12 years	**Safety and efficacy trial (phase II)** ≥ 12 years, QD, 8 weeks S-IGA response: 59.1% vs 11.4% B-IGA response: 40.3% vs 6.8% PSSI-75: 67.2% vs 21.8% PSSI-90: 46.7% vs 3.4% SI-NRS response: 71.0% vs 18.5% PSD change: − 55.0 vs − 27.5 **ARRECTOR (phase III)** ≥ 12 years, QD, 8 weeks Status: in progress (NCT05028582)	
Halobetasol propionate 0.05% foam	Corticosteroid	Age ≥ 12 years	**Safety and efficacy trial (phase III)** ≥ 18 years, BID, 2 weeks IGA response 25.3% vs 3.9%, 30.7% vs 7.4% Safety and efficacy trial (phase IV) 12–17 years, BID, 2 weeks IGA response: 54% HPA suppression: 26.1% (no clinical symptom, normalized 4 weeks after discontinuation) Adrenal suppression and absorption study (phase IV) 12–17 years, BID, 2 weeks Status: results submitted for review (NCT03992261)	Burning, stinging, skin atrophy, telangiectasia, HPA-axis suppression
Tapinarof 1% cream	AhR modulator	Age ≥ 18 years	**PSOARING 1 and 2 (phase III)** ≥ 18 years, QD, 12 weeks PGA response: 35.4% vs 6.0%, 40.2% vs 6.3% PSOARING 3 (phase III) ≥ 18 years, QD, 44 weeks Complete clearance: 40.9% PGA response: 58.2% Mean remittive effect: ~4 months **Pediatric trial (phase III)** 2–17 years, QD, 12 weeks + optional 40 weeks extension Status: in progress (NCT05172726)	Contact dermatitis, folliculitis, headache

AhR aryl hydrocarbon receptor, *BID* twice daily, *FDA* Food and Drug Administration, *HPA* hypothalamic-pituitary-adrenal, *IGA* Investigator's Global Assessment, *B-IGA* body IGA, *I-IGA* intertriginous IGA, *S-IGA* scalp IGA, *PDE-4* phosphodiesterase type 4, *PASI* Psoriasis Area and Severity Index, PGA Physician's Global Assessment, *PK* pharmacokinetic, *PSD* Psoriasis Symptom Diary, *PSSI* Psoriasis Scalp Severity Index, *QD* once daily, *SI-NRS* Scalp Itch Numeric Rating Scale, *WI-NRS* Worst Itch Numeric Rating Scale

Tofacinitib is a selective JAK1 and JAK3 inhibitor that was investigated in the twice-daily application of the 2% ointment formulation for the treatment of plaque psoriasis in adults. Two 4-week phase IIa studies showed good tolerability and safety but modest efficacy relative to the vehicle group [49]. Following this, a larger 12-week phase IIb study was conducted to investigate the once-daily and twice-daily application of tofacitinib 1% and 2% ointment. Clinical improvements were again modest compared with the vehicle group, but pruritus was significantly reduced suggesting its potential use for itch relief. This program development has been discontinued [50].

Brepocitinib is another JAK inhibitor selective for tyrosine kinase 2 and JAK1 that underwent a 12-week phase IIb study investigating different topical concentrations (0.1%, 0.3%, 1.0%, and 3.0% in cream formulations) with once-daily and twice-daily applications for treating mild-to-moderate psoriasis in adult patients. Results showed that brepocitinib cream was well tolerated but failed to show significant efficacy compared with the vehicle group, and this investigative study has since been discontinued [51, 52].

Systemic JAK inhibition for the treatment of plaque psoriasis in adults has also been examined. In a long-term safety and toleratibility study of oral tofacitinib that involved 2867 participants, >10% serious AEs and > 60% non-serious AEs were reported. This study was subsequently terminated [53]. A study to examine the use of topical or systemic JAK inhibitors to treat pediatric psoriasis has not been conducted.

4.3 Additional Therapeutic Agents

Pegcantratinib (SNA-120) is a potent inhibitor of tropomyosin receptor kinase A, which interacts with tyrosine kinases to modulate neurogenic inflammation. Its 0.5% ointment formulation was a drug candidate under investigation in two phase II studies evaluating the safety, efficacy, tolerability, and associated pruritus when trialed as monotherapy as well as in combination with calcipotriene 0.005% ointment against a vehicle for treating psoriasis in patients aged 12 and 18 years, respectively. No results were posted (NCT03322137, NCT03448081). Unfortunately, the investigative pharmaceutical company filed for bankruptcy in 2019 and the drug development has been discontinued [54].

PF-07038124 is a novel PDE-4 inhibitor that is currently under investigation [55]. A 6-week phase IIb study (EMPORIA) was conducted to investigate the once-daily application of PF-07038124 in the 0.1% ointment formulation for its efficacy, safety, tolerability, and pharmacokinetics in treating plaque psoriasis in patients aged 18 years and older. In the pediatric landscape, a 12-week phase IIb study is ongoing with the aim to assess the efficacy, safety, tolerability, and pharmacokinetics of different concentrations (0.01%, 0.03%, 0.06% ointments) in patients with psoriasis aged 12 years and older (NCT04664153, NCT05375955).

5 How Emerging Topical Agents Add to the Conventional Treatments?

The currently available range of topical therapies for pediatric psoriasis highlights our improved understanding of the pathophysiology of psoriasis and identification of effective therapeutic targets over the years. However, side effects and tolerability still limit their use, particularly in the face and intertriginous areas. There is room for improvement in our existing topical armamentarium for pediatric psoriasis. One of the main reasons for the failure of current topical treatments is poor adherence to treatment, either because of side effects or, more commonly, poor tolerability such as irritation or burning sensation. The recent FDA approvals of roflumilast and halobetasol propionate 0.05% foam bring a welcome addition. The FDA approval of tapinarof for adult psoriasis and its ongoing study for pediatric psoriasis is also encouraging. In particular, both roflumilast and tapinarof are non-steroidal options that show great efficacy and tolerability for use in the face and intertriginous areas, which shows great promise to address the gaps in our current list of topical agents for pediatric psoriasis.

Combination therapy has shown great efficacy while reducing the risk of AEs from each topical agent. Rotational therapy of TCS and non-steroidal topical agents is another approach recommended by expert guidelines to reduce AEs and over-reliance on TCS. [2] Combining or rotating the use of TCS with TCIs, vitamin D analogs, tazarotene, emollients, salicylic acid, and coal tar have been studied mainly in adults. Adding new therapies that target different pathogenic pathways should add a synergistic effect. More studies are warranted to examine effective and safe combination therapies in pediatric psoriasis, including the use of novel topical therapies with existing options such as TCS, TCIs, and vitamin D analogs.

Many therapeutic targets, as discussed in the previous section, have been investigated in the endeavor to improve our topical treatment options for psoriasis. While many were discontinued, a few are still being actively investigated. As our understanding of the complex pathogenesis of psoriasis continues to evolve, we are hopeful that more therapeutic targets and pathways may be identified that can enhance our current topical management of pediatric psoriasis.

6 Conclusions

Pediatric psoriasis is common and increasing in prevalence, but traditional topical therapeutic options are still limited in the ability to balance efficacy with side effects and tolerability. Topical therapies play a crucial role as first-line treatments for psoriasis, and they are particularly important in pediatric psoriasis where the proportion of mild cases and involvement of sensitive areas are higher compared with adults. In addition to improvements in conventional TCS, TCIs, and vitamin D preparations, many drugs, including roflumilast and tapinarof, developed based on new mechanisms to minimize side effects, are being presented as novel options for psoriasis treatment. More data from ongoing clinical trials will provide a greater understanding of the efficacy and safety of these novel topical agents in the management of pediatric psoriasis. Efforts are also ongoing to investigate new therapeutic targets and more effective formulations that will continue to improve the clinical management of pediatric psoriasis.

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Declarations

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