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LEADING ARTICLE

New Topical Therapies for Psoriasis

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Abstract
Psoriasis is a chronic immune-mediated skin disease with a significant impact on patients' quality of life. Mild-to-moderate forms of the disease usually require long-term topical treatment, but prolonged use of corticosteroids and vitamin D analogues is limited by adverse effects. With further understanding of psoriasis pathogenesis, new molecules are emerging aiming to fulfil these clinical needs. Tapinarof, an aryl hydrocarbon receptor modulator, has completed a phase III study and demonstrated good efficacy results, even in long treatment courses, with a favourable safety profile. It additionally appears to have a promising remitting effect as patients presented with an average relapsing time of over 3 months. Roflumilast, a phosphodiesterase type 4 inhibitor, also underwent a phase III study with significant lesion improvement and notable pruritus management, and with no reported side effects. Roflumilast was evaluated as an option for intertriginous areas with good outcomes in a small sample, but larger trials are required. The Janus kinase-signal transducer and activator of transcription pathway has been targeted in recent clinical investigations with promising options, currently with brepocitinib pending phase IIb results. Ongoing preclinical studies involving interleukin-2 inhibition, RNA modulators and amygdalin analogues may lead to forthcoming clinical trials. New topical drugs are successfully emerging and future research comparing them to classical options will dictate their clinical role in the treatment of psoriasis.

Key Points

There is currently a lack of options for long-term topical treatment for mild-to-moderate psoriasis; new molecules are emerging aiming to fulfil these clinical needs.

Tapinarof, an aryl hydrocarbon receptor modulator, is an effective new topical drug with the advantage of inducing a prolonged remission time but with a frequent incidence of folliculitis.

Roflumilast, a phosphodiesterase type 4 inhibitor, has been shown to improve skin lesions and ameliorate itch, also with good results in skin folds and no associated side effects.

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1 Introduction

Psoriasis is a chronic immune-mediated disease affecting around 3% of the world population. It is associated with multiple comorbidities, carrying a heavy impact on patients' quality of life [1].

Depression and anxiety are over three times more frequent in patients with psoriasis and their global well-being is constantly threatened by pruritic, painful and socially stigmatising skin lesions [2–4].

Plaque psoriasis is the most common form of the disease, accounting for 80% of the cases. It presents with sharply demarcated, erythematous scaly plaques, often symmetrically distributed that typically follow a relapsing and remitting course. Other variants include guttate, erythrodermic and pustular psoriasis [1].

Psoriasis arises from a complex immunological impairment in genetically susceptible individuals. Environmental stimuli or loss of self-tolerance via autoantibodies trigger plasmacytoid dendritic cells to secrete inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interferon (IFN)-α, which activate myeloid dendritic cells to release interleukin (IL)-23. Interleukin-23 promotes the proliferation of T helper (Th) 17 and Th22 cells, which enhance IL-17 and IL-22 production, respectively.

Interleukin-17 is the major effector cytokine in psoriasis and together with TNF-α induce the expression and release of many keratinocyte proteins (including hBD2, LCN2, LL37/cathelicidin), activate other inflammatory signals (such as STAT1 and nuclear factor kappa-light-chain-enhancer of activated B cells) and trigger keratinocytes to secrete neutrophil-recruiting factors such as CXCL1, CXCL2, CXCL3, CXCL5 and CXCL8 (IL-8). Interleukin-22 works together with IL-19 and IL-36 playing an essential role in epidermal hyperplasia and parakeratosis. Myeloid dendritic cells also promote differentiation of Th17 cells, leading to a positive feedback loop that sustains the IL-23/IL-17 signalling pathway [5–7].

Although there is no consensus regarding the definition of mild, moderate and severe psoriasis, mild-to-moderate forms account for about 80% of patients. Usually, psoriasis affecting less than 10% of body surface area can be managed with topical treatments [1, 8]. Nonetheless, it is essential to note that a milder manifestation of the disease may also be associated with a high impact on quality of life and prompt and effective treatment is imperative.

When optimised topical treatment is not enough to control the disease, it becomes necessary to escalate to systemic options, which entail a greater risk of adverse effects than topical treatments. The more effective topical drugs become, the fewer patients will need to start on systemic treatment, reducing systemic exposure to the drugs applied. Extensive forms of the disease may require a combination therapy of systemic and topical agents to treat persistent plaques and reach full resolution [9].

Moreover, the extent of lesions is not the only matter concerning a patient's management. Although psoriatic lesions are more frequently found on extensor surfaces, lower back and scalp, other anatomic areas with a thinner and more sensitive skin such as body folds and facial and genital regions are commonly affected and carry a greater psychological impact and bigger challenges regarding treatment options [10, 11]. The aim of this review is to provide a synthesised overview of the current state of knowledge on the topical treatment of psoriasis, reflecting on currently existing gaps and future research directions.

2 Currently Available Topical Treatments

Corticosteroids and vitamin D analogues remain the main topical therapeutic options for patients with mild-to-moderate psoriasis, and their combination is more effective than each one in monotherapy [12, 13]. Topical corticosteroids exert anti-inflammatory, anti-proliferative and locally vasoconstrictive effects through down-regulation of genes coding proinflammatory cytokines, making them effective in psoriasis. Being a chronic disease, psoriasis often needs a long-term maintenance treatment to avoid relapsing. Side effects such as skin atrophy, telangiectasia and striae limit the long-term use of this therapeutic option, particularly in areas of sensitive thin skin such as on the face and intertriginous areas [14, 15].

Vitamin D analogues (calcipotriol and tacalcitol) inhibit keratinocyte proliferation while promoting their sequential differentiation through each epidermal layer. They also modulate the humoral and cellular immune system by supressing proinflammatory T-cell cytokine production. However, their efficacy as monotherapy is limited, and skin irritation is a frequent side effect that leads to treatment discontinuation [14, 15].

When used in combination, corticosteroids counteract the irritant effects of vitamin D analogues, and atrophy is limited by vitamin D analogues. New formulations are still being developed in order to obtain the best efficacy and safety profile [16, 17].

Tazarotene is a topical retinoid that works as a keratolytic agent inhibiting keratinocyte proliferation and abnormal differentiation, but its use is also limited by local irritant symptoms such as itching and burning. Its association with potent corticosteroids was shown to be more efficient and better tolerated [18]. New formulations using lower doses have allowed increased efficacy with almost no side effects, even after continuous treatment up until 24 weeks [19]. Halobetasol helps soothing the irritant effects of tazarotene and the latter is able to reverse the atrophic effects of the potent corticosteroid [19].

Topical calcineurin inhibitors such as pimecrolimus and tacrolimus have been used to treat facial, genital and intertriginous psoriasis. They block T-cell activation by inhibiting IL-2 and IFN-γ synthesis. Topical calcineurin inhibitors are particularly useful as a maintenance therapy considering the long-term therapy side effects of topical corticosteroids, but are used off-label [10, 11, 20].

Nevertheless, despite the aforementioned therapeutic options, there is often a lack of patient satisfaction and high rates of non-compliance regarding topical psoriasis treatment, indicating the urgent need for therapeutic alternatives. The main reasons behind poor compliance include low efficacy, unsatisfying cosmetic results, time taken to apply the treatment and a poor doctor-patient relationship [21].

Thus, because of these unmet needs for the topical treatment of mild-to-moderate psoriasis, new effective molecules with an adequate long-term safety profile are needed, as well as the possibility of being formulated with a convenient vehicle, optimising a patient's compliance. Greater understanding of the pathogenesis of psoriasis has led to highly effective systemic treatments, now widely used in the most severe forms of the disease. Topical treatments aiming at new therapeutic targets are emerging [20, 22].

3 Aryl Hydrocarbon Receptor (AhR) Modulator

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor expressed in keratinocytes, which has been shown to be increased in patients with psoriasis. Aryl hydrocarbon receptor signalling regulates the terminal differentiation of Th17 and Th22 lymphocytes. Aryl hydrocarbon receptor ligands range from endogenous molecules such as heme and arachidonic acid metabolites to dietary and environmental particles [23–25].

3.1 Topical Tapinarof

In 2012, clinical trials started to explore AhR-modulating agents, commencing with WBI-1001, a nonsteroidal anti-inflammatory topical molecule able to suppress Th17-cell differentiation and downregulate cytokines such as IL-17, IL-22 and IL-23. A phase IIb trial with WBI-1001 was conducted with 61 patients, and the results suggested a fast reduction in psoriasis severity and a significant reduction in disease extension. At week 12, the affected body surface area decreased by almost 80% from baseline for patients randomised to WBI-1001, while for patients receiving placebo the affected area expanded [26].

This molecule was subsequently incorporated into a different formulation for better stability, resulting in tapinarof. Beyond the immunological role, tapinarof has been shown to normalise skin cell differentiation, improving the skin barrier [23, 26].

A phase IIb randomised study evaluated the efficacy of tapinarof in mild-to-moderate plaque psoriasis vs a vehicle without an active ingredient [27, 28]. The change in Physician Global Assessment (PGA) score and the proportion of subjects achieving a ≥ 50%, ≥ 75% and ≥ 90% reduction in Psoriasis Area and Severity Index (PASI) scores from baseline were evaluated [2]. Six groups of patients were evaluated through 12 weeks of application of tapinarof 1% twice daily, 1% once daily, 0.5% twice daily and 0.5% once daily, in comparison to two control groups that applied the vehicle cream twice or once daily (Table 1).

At the end of the treatment period, PGA response rates were significantly higher in the groups receiving tapinarof cream in comparison to those receiving the vehicle. Subjects treated with tapinarof 1% cream showed higher response rates than the 0.5% groups, but application twice daily was only slightly more effective, which can simplify the therapeutic scheme and improve adherence. Lesions treated with tapinarof started to clinically improve by week 2. At week 16, 4 weeks after stopping treatment, PASI evaluation of tapinarof groups remained significantly superior to vehicle comparators [27, 28].

According to this trial, tapinarof cream was relatively well tolerated. Folliculitis and contact dermatitis were the most commonly reported side effects, whether considered related or non-related to treatment. Treatment-related folliculitis was reported in 15 patients in tapinarof groups (n = 152) vs one patient in the vehicle groups (n = 75). Contact dermatitis was reported in 12 patients, all in tapinarof groups. Adverse effects led to permanent discontinuation of 10% of patients treated with tapinarof, with contact dermatitis being the most common [27, 28].

Two phase III, identical randomised studies evaluating tapinarof 1% cream in psoriasis have been recently presented: PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980). These were 12-week double-blind trials both including a total of over 1000 subjects, comparing once-daily application of tapinarof 1% cream with a vehicle cream [29, 30].

Table 1 Efficacy of topical taparinof in a phase IIb trial in patients with mild-to-moderate psoriasis

	Tapinarof 1% BID n = 27	Tapinarof 1% QD n = 29	Tapinarof 0.5% BID n = 32	Tapinarof 0.5% QD n = 35	Vehicle 1% BID n = 26	Vehicle 0.5% QD n = 25
PGA response[b]	65%[a]	56%[a]	46%[a]	36%[a]	11%[a]	5%[a]
PGA variation, mean (SD)		− 1.7 (1.0)[a]	− 1.7 (1.1)[a]	− 1.3 (0.8)[a]	− 0.5 (0.8)[a]	− 0.4 (0.7)[a]
PASI50	83%[a]	92%[a]	85%[a]	71%[a]	32%[a]	10%[a]
PASI75	65%[a]	56%[a]	46%[a]	46%[a]	16%[a]	5%[a]
PASI90	39%[a]	40%[a]	31%[a]	18%	0%	0%

[27, 28] Presented data follow a 12-week treatment period

BID treatment application twice a day, *PASI50* proportion of subjects with a ≥ 50% improvement in Psoriasis Area and Severity Index from baseline at week 12, *PASI75* proportion of subjects with a ≥75% improvement in Psoriasis Area and Severity Index from baseline at week 12, *PASI90* proportion of subjects with a ≥ 90% improvement in Psoriasis Area and Severity Index from baseline at week 12, *PGA* Physician Global Assessment, *QD* treatment application once a day, *SD* standard deviation

[a]Statistically significant values for a 95% confidence interval

[b]Percentage of patients who achieved a PGA score of 0 or 1 and a minimum 2-grade improvement from baseline

Respectively in PSOARING 1 and 2, 35.4% and 40.2% of the tapinarof group achieved the PGA primary goal PGA score of 0 or 1 and a minimum 2-grade improvement from baseline, vs 6.0% and 6.3% in the vehicle group. Furthermore, 36.1% and 47.6% in the tapinarof group vs 10.2% and 6.9% in the vehicle group reached PASI75 (Table 2). The safety profile was globally good, but local adverse effects such as folliculitis and contact dermatitis were reported (Table 3). Folliculitis was mainly of mild-to-moderate severity, but it was reported in 20.6% and 15.7% of tapinarof group participants. Despite low discontinuation rates because of side effects (around 5%), the mechanism behind these adverse effects is under study [29, 30].

At the end of the 12-week treatment, qualified subjects (91.6%) entered a separate long-term safety and efficacy study for an additional 40 weeks of treatment with 1% tapinarof cream followed by a 4-week follow-up period, which led to PSOARING 3 (NCT04053387). Patients with a PGA score of 0 discontinued treatment and were closely monitored. If the disease worsened (PGA ≥ 2), tapinarof was reintroduced until the patient achieved a PGA score of 0. According to information revealed at the European Academy of Dermatology and Venereology 30th Congress in September of 2021, 58.2% of subjects who entered PSOARING 3 with a PGA score of at least 2 reached a PGA score of 0 or 1, suggesting a therapeutic effect beyond week 12 of treatment. Complete disease clearance was achieved by 40.9% of the patients at least once during this study [31]. Another interesting and promising detail about this drug is its possible remitting effect, which was evaluated through the duration of efficacy maintenance (PGA score 0 or 1) while off therapy, after achieving complete disease clearance (PGA score of 0). According to presented results, for subjects entering with, or achieving at any time, a PGA score of 0 ($n = 312$), the mean time to disease relapsing after treatment discontinuation was approximately 130 days. Additionally, there seems to be no tachyphylaxis over time while receiving therapy as the durability of response was up to 52 weeks. Regarding safety and tolerability, data showed similar results as previous studies, reporting cases of mild-to-moderate folliculitis and contact dermatitis with low related discontinuation rates (1.2% and 1.4%, respectively). While promising, these data still need to be peer reviewed [31].

3.2 Topical Benvitimod

Benvitimod 1% carries the same active principle as tapinarof with different excipients. It requires two daily applications.

A phase III clinical trial was conducted with 686 patients for 12 weeks evaluating the efficacy and safety of benvitimod cream in comparison to calcipotriol 0.005% ointment and a placebo [32]. A PGA score of 0 or 1 was achieved in 66.3% of patients receiving benvitimod and in 63.9% of patients receiving calcipotriol, both significantly superior to the vehicle group (33.5%). In contrast to most studies, a PGA grade improvement from baseline was not part of the endpoint. Not considering PGA variation can overestimate an improvement if a large percentage of enrolled patients present with a baseline PGA score of 2. A significantly higher proportion of patients receiving benvitimod (50.4%)

Table 2 Efficacy of topical psoriasis treatments

Clinical trial	Trial phase	Evaluated sample	PGA response rate (%)	PASI75 (%)
Tapinarof 1% (PSOARING 1)	III	Treatment ($n = 340$)	35.4	36.1
QD, 12 weeks [29]		Vehicle ($n = 170$)	6.0	10.2
Tapinarof 1% (PSOARING 2)	III	Treatment ($n = 343$)	40.2	47.6
QD, 12 weeks [29]		Vehicle ($n = 172$)	6.3	6.9
Roflumilast 0.3% (DERMIS-1)	III	Treatment ($n = 286$)	42.4	41.6
QD, 8 weeks [37]		Vehicle ($n = 153$)	6.1	7.6
Roflumilast 0.3% (DERMIS-2)	III	Treatment ($n = 290$)	37.5	39.0
QD, 8 weeks [37]		Vehicle ($n = 152$)	6.9	5.3
Tofacitinib 2%	IIb	Treatment ($n = 70$)	18.6	17.9
QD, 8 weeks [48]		Vehicle ($n = 74$)	8.1	8.3
Calcipotriol + betamethasone[a]	II	Treatment ($n = 141$)	54.6	50.4
QD, 4 weeks [17]		Vehicle (N/A)		

Results are presented for independent randomised controlled trials, and calcipotriol plus betamethasone is included for reference to an existing effective topical treatment

N/A unavailable information, *PASI75* proportion of subjects with ≥ 75 % improvement in Psoriasis Area and Severity Index from baseline at week 12, *PGA response rate* proportion of subjects with a PGA score of clear or almost clear (0 or 1) and a ≥ 2-grade improvement in PGA score from baseline, *QD* once-a-day application

[a]Aerosol foam formulation of a fixed combination of calcipotriene 0.005% plus betamethasone dipropionate 0.064%

Table 3 Preliminary safety data for topical tapinarof and roflumilast

		Incidence of TEAEs	Discontinuation due to AEs	Most common TRAEs
Tapinarof 1% QD, 12 weeks PSOARING 1 [29, 30]	Treatment $n = 340$	171 (50.3%)	19 (5.6%)	Folliculitis: 70 (20.6%) Contact dermatitis: 13 (3.8%) Pruritus: 4 (1.2%)
	Vehicle $n = 170$	38 (22.4%)	0 (0.0%)	Folliculitis: 2 (1.2%) Contact dermatitis: 1 (0.6%)
Tapinarof 1% QD, 12 weeks PSOARING 2 [29, 30]	Treatment $n = 343$	187 (54.5%)	20 (5.8%)	Folliculitis: 54 (15.7%) Contact dermatitis: 16 (4.7%) Pruritus: 2 (0.6%)
	Vehicle $n = 172$	45 (26.2%)	1 (0.6%)	Folliculitis: 1 (0.6%)
Roflumilast 0.3% QD, 8 weeks DERMIS-1 [38]	Treatment $n = 286$	72 (25.2%)	5 (1.7%)	Diarrhoea: 10 (3.5%) Hypertension: 5 (1.7%) Headache: 3 (1.0%) Nasopharyngitis: 5 (1.7%)
	Vehicle $n = 153$	36 (23.5%)	2 (1.3%)	Diarrhoea: 0 (0.0%) Hypertension: 6 (3.9%) Headache: 2 (1.3%) Nasopharyngitis: 3 (2.0%)
Roflumilast 0.3% QD, 8 weeks DERMIS-2 [38]	Treatment $n = 290$	75 (25.9%)	1 (0.3%)	Diarrhoea: 8 (2.8%) Hypertension: 4 (1.4%) Headache: 11 (3.8%) Nasopharyngitis: 1 (0.3%)
	Vehicle $n = 152$	28 (18.4%)	2 (1.3%)	Diarrhoea: 0 (0.0%) Hypertension: 0 (0.0%) Headache: 1 (0.7%) Nasopharyngitis: 1 (0.7%)

Data derived from two independent, phase III, randomised clinical trials

AE adverse effects, *QD* once a day, *TEAEs* adverse effects emerging on or after first dose of the study drug, *TRAEs* treatment-related adverse effects

achieved a PASI75 response compared with patients receiving calcipotriol (38.5%) or placebo (13.9%). Adverse effects were reported in almost 50% of the benvitimod group, most commonly pruritus (in 21.2%), contact dermatitis and folliculitis [32].

A post-treatment follow-up of 59 patients corroborated the remitting effect observed for tapinarof. Thus, 29 patients (49%) maintained remission until week 52, and the average time to recurrence among the other patients was 36 weeks [32].

4 Phosphodiesterase Type 4 (PDE-4) Inhibitors

Overexpression of phosphodiesterase type 4 (PDE-4) also appears to contribute to the pathogenesis of psoriasis. This enzyme is highly expressed in immune cells in which it is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), a key intracellular second messenger in several signal transduction mechanisms. One of the most well-described and central roles of cAMP is the activation of protein kinase A, which stimulates the synthesis of anti-inflammatory cytokines through phosphorylation of cAMP-responsive element binding protein and activation of transcription factor 1. In contrast, protein kinase A blocks transcription factors of proinflammatory cytokine synthesis such as B-cell lymphoma 6 protein and nuclear factor kappa-light-chain-enhancer of activated B cells. The imbalance we observe in these patients favours proinflammatory cytokine synthesis and immune cell proliferation [33, 34].

Phosphodiesterase type 4 activity has been shown to be higher in psoriatic skin. The inhibition of PDE-4 increases cAMP levels, leading to a downregulation of immune modulators involved in psoriasis pathophysiology such as

TNF-α, IFN-γ, IL-17 and IL-23. In fact, apremilast, an oral PDE-4 inhibitor, is already used for the treatment of moderate-to-severe psoriasis [35].

4.1 Topical Roflumilast

A phase I, randomised single-centre small study was conducted comparing the clinical effects of creams containing roflumilast 0.5%, TAK-084 0.5% or TAK-084 5% [36]. TAK-084, like roflumilast, is a PDE-4 inhibitor. The control arms were active comparators (betamethasone valerate 0.1% cream and calcipotriol 0.005% cream) and a vehicle cream. Over a 3-week treatment period, 15 patients received a once-daily application of all six creams to different areas of psoriatic plaques, covered by a hydrocolloid dressing. Both roflumilast and TAK-084 showed statistically significant reductions in skin infiltrate thickness when compared with the vehicle group, and outcomes for the two TAK-084 formulations were dose dependent. Roflumilast and TAK-084 5% also performed better than calcipotriol but they were inferior to corticosteroids, although the mean change in skin infiltrate thickness for roflumilast (− 237.1 µm) was very close to that for betamethasone (− 286.9 µm) [36].

Subsequently, a randomised, double-blind phase IIb trial was conducted evaluating 331 patients with mild-to-moderate psoriasis [34]. Patients were split into three groups in which roflumilast 0.3% cream, roflumilast 0.15% cream or a vehicle cream were applied once daily to all psoriasis lesions for a period of 12 weeks. At week 6, 28% of the patients in the roflumilast 0.3% group and 23% of those in the roflumilast 0.15% group reached a PGA score of clear or almost clear (a score of 0 or 1), which was considered the primary outcome. Considering the vehicle group, only 8% of patients reached this result. At the end of week 12, 38% and 32% of the patients randomised to roflumilast 0.3% and 0.15% groups, respectively, achieved a PGA score of 0/1 [34].

A subset of 47 patients with intertriginous involvement were separately evaluated though an intertriginous-area PGA score and, by week 6, a score of 0 or 1 plus a 2-grade improvement was achieved in 73% of the patients in the roflumilast 0.3% group and in 29% of those in the vehicle group. Out of 15 patients within the 0.3% group, 14 had an intertriginous-area PGA score of 0 after 12 weeks, while in the vehicle group only 3 out of 17 presented with this result. The incidence of intervention-related side effects in this subset was similar in active treatment and vehicle groups [34].

Twin phase III randomised vehicle-controlled studies of roflumilast 0.3% (DERMIS-1, NCT04211363 and DERMIS-2, NCT04211389) were completed towards the end of 2020. Over 800 participants with chronic plaque psoriasis were randomly assigned to apply for 8 weeks once daily of either the roflumilast cream or the vehicle cream. Pivotal data were released and presented excellent results. At the end of week 8, patients in the roflumilast arms reached a PGA response of 42.4% and 37.5% compared with 6.1% and 6.9% for patients in the vehicle arms, for DERMIS-1 and DERMIS-2, respectively (Table 2) [37]. Pruritus improvement was evaluated through a scale from 0 (no itch) to 10 (worst imaginable itch), WI-NRS. Among roflumilast-treated patients with a baseline WI-NRS score of at least 4, over two-thirds achieved a 4 point or greater reduction in WI-NRS, statistically significant against the vehicle since week 2 in DERMIS-2 and week 4 in DERMIS-1. This was also reflected in the quality-of-life (Dermatology Life Quality Index) assessment. Roflumilast cream demonstrated low rates of application-site adverse effects and it was well tolerated. Regarding the safety profile, the most reported side effects were hypertension, headache, diarrhoea and nasopharyngitis. All mentioned side effects were comparably mentioned inn roflumilast-treated and vehicle-treated patients, with the exception of diarrhoea that was reported in 18 patients (ten from DERMIS-1 and eight from DERMIS-2) from the roflumilast arms against none from the vehicle arms (Table 3) [38]. Nevertheless, these data still need to be peer reviewed. A 24-week extension of the preceding studies is presently ongoing to evaluate long-term safety (NCT04286607). Its use is also being studied for children in phase II trials (NCT04655313, NCT04746911) (Table 4).

4.2 Topical Crisaborole

Crisaborole (AN-2728) is a topical PDE-4 inhibitor already approved for atopic dermatitis. The efficacy of crisaborole for the treatment of of intertriginous, anogenital and facial psoriasis was assessed in a small randomised controlled trial involving 21 patients from a single tertiary care centre [39]. Crisaborole 2% ointment was applied twice a day and compared to a vehicle ointment.

After 4 weeks of treatment with crisaborole 2% ($n = 14$), there was a significant improvement in erythema, plaque elevation/induration and scaling in comparison to the vehicle group. After 8 weeks, lesional clearance was achieved in over 70% of these subjects and there were no reports of adverse skin reactions [39]. Despite the good results in small sample-sized studies, further research for its application in psoriasis was not pursued.

5 Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) Inhibitors

Janus kinases (JAKs) are a subset of cytoplasmatic protein tyrosine kinases involved in cytokine receptor signalling. Cytokines bind to a cell receptor, triggering JAK

Table 4 Ongoing clinical trials involving new topical treatments for psoriasis

Mechanism of action	Drug	Phase	Clinical trial	Status
AhR receptor modulation	Tapinarof 1%	III	NCT04053387 (PSOARING 3)	Completed
PDE-4 inhibitor	Roflumilast 0.3%	III	NCT04286607 (DERMIS-OLE)	Enrolling by invitation (ARQ-151-301 or 302)
PDE-4 inhibitor	Roflumilast 0.3%	II	NCT04655313, NCT04746911	Recruiting (paediatric)
PDE-4 inhibitor	Roflumilast 0.3%	II	NCT04549870	Recruiting (adults)

AhR aryl hydrocarbon receptor, *PDE-4* phosphodiesterase type 4

phosphorylation and subsequent activation of signal transducer and activator of transcription (STAT) proteins. Different JAKs associate with specific cytokine receptors: JAK1, for example, is associated with IFNα/γ, IL-6 and IL-22 receptors, JAK2 and TYK-2 are triggered by IL-12 and IL-23, and JAK3 is crucial in lymphocyte function activated by IL-2 and IL-21. Respective activated STATs are then able to move into the cell nucleus and modulate gene expression [40–42].

Preclinical studies have identified several cytokines involved in the pathogenesis of psoriasis that signal through the JAK/STAT pathway. Selective JAK inhibition has been shown to reduce keratinocyte proliferation and inflammation, making it a promising therapeutic strategy [40, 43].

5.1 Topical Ruxolitinib

Ruxolitinib (INCB018424) selectively inhibits JAK1 and JAK2, blocking signal transduction of multiple proinflammatory cytokines. Topical ruxolitinib is currently under regulatory review by the US Food and Drug Administration for the treatment of atopic dermatitis. With regard to psoriasis, preclinical studies in mice showed that topical ruxolitinib reduced lymphocytic infiltration, keratinocyte proliferation and acanthosis, which led to further research [40].

A first clinical trial with 29 patients evaluated, in five different cohorts, a once-a-day application of ruxolitinib 0.5% and 1.0% against a vehicle, and a twice-a-day application of ruxolitinib 1.5% in comparison to a vehicle, calcipotriene and betamethasone dipropionate [44]. In each patient, two similar psoriatic plaques with comparable lesion scores were chosen, one treated with ruxolitinib and the other with the respective comparator, according to an assigned cohort. At the end of 28 days, both the 1% and the 1.5% creams improved lesion thickness, erythema and scaling and reduced the lesion area compared with placebo, with a lesion severity score reduction greater than 50%. Ruxolitinib 1.5% even performed slightly better than calcipotriene. Adverse effects including stinging and itching at the application site were all mild and reported equally in vehicle-treated lesions [44].

Another small study analysed five cohorts of five patients each to evaluate the safety and efficacy of ruxolitinib 1.5% when applied in different concentrations and different percentages of body surface area [45]. After 28 days, both lesion severity scores and lesion areas decreased in about 50%. The PGA score also improved in all cohorts, with the greatest improvement seen in the 1.5% twice-daily treatment groups. Histological evaluation before and after treatment showed a significantly thinner epidermis, decreased parakeratosis, restoration of granular layer and a decreased inflammatory infiltrate. Systemic absorption was consistently low and safe, even when applied in a 1.5% concentration, twice a day, in 14–20% of body surface area [45]. No further studies were developed on this drug for psoriasis.

5.2 Topical Tofacitinib

Tofacitinib (CP-690550) selectively inhibits JAK1 and JAK3 and has been studied as an oral treatment for psoriasis and psoriatic arthritis. Despite positive outcomes of two phase III trials in patients with psoriasis [46], the US Food and Drug Administration declined approval of this drug for psoriasis because of an unfavourable safety/efficacy balance. To overcome this obstacle, tofacitinib has been studied as a topical treatment.

A phase IIa, randomised, double-blind, vehicle-controlled trial evaluated the efficacy and safety of tofacitinib 2% in two ointment formulations [47]. For 4 weeks, 71 patients with mild-to-moderate psoriasis applied the assigned ointment (tofacitinib or vehicle) on a targeted plaque, twice a day. An improvement in the target plaque severity score was statistically significant for only one of the formulations compared to the placebo group and the degree of improvement was modest and probably with a limited clinical impact. Even though systemic concentrations of tofacitinib were measurable when applied to a treatment area of approximately 1.5% of body surface area, levels were considered very low and safe. Tofacitinib was well tolerated and no patient discontinued because of side effects [47].

For a better understanding of these initial results, a large phase IIb randomised trial with 435 patients was performed for 12 weeks to study tofacitinib 1% and 2% ointment when

applied once and twice a day [48]. At week 8, the PGA response of clear (0) or almost clear (1) with a ≥ 2 grade improvement from baseline was 18.6% for tofacitinib 2% once a day and 22.5% for tofacitinib 2% twice a day, in comparison to 8.1% and 11.3% for respective vehicles (Table 2). This mild improvement plateaued after week 8, and by week 12 no significant difference was observed between tofacitinib groups and respective vehicle groups. However, clinical impact especially regarding pruritus was strongly suggested by the Itch Severity Item score change assessment. Application-site adverse effects were reported more frequently in the vehicle arms, with "psoriasis" being the most common [48]. Because of the modesty of the efficacy results, research regarding this drug was abandoned.

5.3 Topical Brepocitinib

Brepocitinib (PF-06700841) is a TYK2/JAK inhibitor that was under investigation as an oral drug. A phase II study (NCT02969018) was conducted with good efficacy outcomes, but safety concerns were raised [49]. Further development as an oral treatment has been discontinued. Instead, brepocitinib is now being investigated as a topical option. A phase IIb trial to study different concentrations of topical PF-06700841 applied once or twice a day, and involving 344 patients (NCT03850483), was completed in April, 2021. This trial included a 6-week screening period, a 12-week treatment period, and 4 weeks of a follow-up evaluation. Results have not been published yet.

6 Retinoic Acid Receptor-Related Orphan Receptor-γ (RORγ) Agonists

GSK2981278 is a highly potent and selective inverse agonist of retinoic acid receptor-related orphan receptor-γ (RORγ). By interfering with this receptor, the molecule influences the main transcription pathways involved in Th17 cell differentiation and expression. Preclinical data showed GSK2981278 significantly inhibits Th17 cytokine production, in in vitro and in human tissue-based systems [50, 51]. A small, phase I, randomised controlled trial was conducted with 15 participants to assess the efficacy of GSK2981278 in reducing the infiltrate thickness of psoriatic plaques, and safety [52]. Six topical products were evaluated: GSK2981278 ointment (0.03%, 0.1%, 0.8% or 4%), a vehicle and betamethasone valerate 0.1% cream as a positive control. Each treatment was applied to all participants, 6 days a week, to different test sites located on psoriasis plaques, which allowed an intra-individual comparison. At the end of 19 days, only the positive control showed a reduction in infiltrate thickness. The lack of effect observed in this study may be explained by a short treatment period, a small area of application or RORγ may not be a viable target for the topical control of psoriasis if the pathogenesis of the disease involves its systemic activity. Further studies are required for clarification [52].

7 Additional Targets for Topical Treatment

7.1 Interleukin-2 (IL-2) Inhibition

Interleukin-2 helps regulate T-cell activation and proliferation through IL-2-inducible T-cell kinase. BMS-509744 is a small molecule that binds to and inhibits IL-2-inducible T-cell kinase, that is being investigated as a promising psoriasis treatment. Preclinical investigations on the effect of topically administered BMS-509744 have been recently conducted in an imiquimod-induced lesion mouse model. Results appear promising; decreased lesion thickness was observed, histologically supported by a reduction in the inflammatory cell infiltrate and lower messenger RNA levels of Th17-related cytokines (IL-17A, IL-17F and IL-22) [53].

7.2 RNA Modulation

MicroRNAs (miRNAs) are short noncoding RNA sequences known to regulate gene expression. They supervise keratinocyte and T-cell proliferation and differentiation. Studies have suggested that patients with psoriasis present with different levels of miRNA expression when compared with subjects without this disease; downregulation of some subtypes of miRNAs and upregulation of others [54–56].

With further knowledge about the behaviour of miRNAs, these small RNA sequences could be designed to modulate disease pathophysiology. Topical delivery has been shown to be feasible through different carriers [56].

MicroRNA-210 was shown to be highly expressed in psoriatic skin lesions and CD4+ T cells from both patients with psoriasis and psoriasis-like mouse models [57]. Based on this knowledge, a study evaluated topical administration of a nanocarrier gel containing miRNA-210 antisense in a mouse model. Topical treatment with miRNA-210 antisense significantly reduced miRNA-210 expression in skin lesions and T cells and ameliorated erythema, scaling, acanthosis and inflammatory infiltrate in psoriatic mice [58]. Further studies are needed.

7.3 Amygdalin Analogue

Thymic stromal lymphopoietin is an inflammatory cytokine released when keratinocytes are under stress, and is highly expressed in the epidermis of patients with psoriasis.

Synergically with the T-cell-derived CD40 ligand, it promotes IL-23 production by dendritic cells, adding to the immune cascade [59].

Amygdalin analogues are stable molecules derived from vitamin B_{17} that have anti-inflammatory properties and good skin penetration in preliminary studies. Recently, a study with genetically engineered mouse models with psoriasis-like lesions evaluated the efficacy of FIB-116, an amygdalin analogue, following topical application [60]. After 15 days, mice treated with FIB-116 had a macroscopic improvement in lesion severity with respect to inflammation, plaque size and the number of affected areas in comparison to untreated or vehicle-treated mice. Microscopically, a reduction in psoriasis-like histological features was also reported (acanthosis, hyperkeratosis, parakeratosis and inflammatory infiltrate). This mechanism of action of the drug seems to correlate with a reduction in thymic stromal lymphopoietin gene expression, inhibiting keratinocyte proliferation and proinflammatory response. Additionally, FIB-116 was shown to reduce several cytokines associated with psoriasis pathogenesis, not only locally in lesional skin (IL-17α, TNF-α, IFN-γ) but also systemically in mice serum (IL-17α, IL-6) [60]. Clinical trials are required to understand potential applicability.

8 Discussion

Psoriasis is a chronic inflammatory disorder that severely interferes with patients' quality of life. It often needs prolonged maintenance treatment periods because of its relapsing and remitting behaviour. Most patients have localised disease and have no indication for systemic therapy as a first approach, but when topical options are insufficient to control the disease, it becomes necessary to escalate to systemic treatment. Systemic drugs currently used for psoriasis are very effective but carry a bigger risk of adverse effects than topical treatments. Moderate-to-severe forms of the disease may require both systemic and topical agents in combination to reach full resolution [1, 8].

Topical corticosteroids alone or in association with vitamin D analogues are effective in the treatment of psoriasis, but long-term use is limited by potential side effects [1, 40]. Even so, they remain the mainstay therapy for these patients and new improved formulations continue to be developed [16, 17].

Progress in the understanding of the pathogenesis of psoriasis has allowed the development of new targeted topical molecules, which may allow the use of highly effective drugs, with reduced systemic exposure. The psoriasis immunological cascade is mediated by a myriad of inflammatory cytokines, as well as some intracellular signalling pathways, namely AhR, JAK-STAT and PDE-4, which have been the focus of the latest research.

The JAK-STAT inhibitors were initially under investigation as systemic options for psoriasis. Although systemic use has proved effective, safety concerns limited their approval. Topical JAK inhibitors such as ruxolitinib and tofacitinib were abandoned because of disappointing efficacy results. Brepocitinib, a TYK2/JAK 1 inhibitor, is the most recent option in this class of drugs, but phase IIb results are still unpublished.

Tapinarof, an AhR modulator, and roflumilast, a PDE-4 inhibitor, are the most promising topical molecules under investigation, having shown a favourable efficacy and safety profile in large phase III studies. Preliminary results of a 12-week treatment with tapinarof 1% cream suggested significantly superior efficacy in comparison to the vehicle.

An extension of this trial for 40 weeks allowed for further long-term conclusions. Patients who still presented with skin lesions and maintained treatment with tapinarof continued to improve, suggesting longer treatment courses maintain therapeutic benefits. An interesting remitting effect of this drug was also observed, considering the median relapsing time after stopping topical treatment among patients with no signs of psoriasis plaques was superior to 3 months.

Tapinarof was globally well tolerated and safe, but folliculitis is a prevalent adverse effect that can affect up to 20% of patients. This could be an important limitation for its applicability, particularly in intertriginous areas. It is important to understand the mechanism behind folliculitis as a side effect and whether it can be managed [29, 31]. To date, no studies compared the performance of tapinarof with a positive control such as a topical corticosteroid, which would be essential for further conclusions regarding its clinical applicability.

Roflumilast 0.3% also presented a favourable efficacy profile after 8 weeks of treatment. It improved plaque severity and a significant impact on pruritus was reported. The overall incidence of adverse effects and consequent discontinuation were low and the local tolerability profile was good. A 24-week extension trial is currently ongoing for longer term conclusions [37].

A phase I small study compared roflumilast 0.5% to betamethasone valerate 0.1% and calcipotriol 0.005%. Results pointed to a superiority of roflumilast over calcipotriol but not over corticosteroids. Additional larger studies are required to compare new and upgraded formulations of roflumilast with isolated potent corticosteroids and combinations with vitamin D analogues and tapinarof [36].

Intertriginous areas are the most challenging considering the side effects of the current options and, so far, few studies have focused specifically on this subtype of psoriasis. Roflumilast was evaluated vs a vehicle in 47 patients with intertriginous involvement, and good efficacy results were suggested [34]. Considering these results and the mild local side effects, roflumilast could become a first-line option for

this form of psoriasis if larger trials support these outcomes. There are preclinical studies on prospective topical agents such as IL-2 inhibitors, amygdalin analogues and microRNAs, but little information is available and further investigation is required.

9 Conclusions

Breakthrough knowledge on psoriasis pathogenesis is allowing the discovery of new therapeutic targets and promising topical drugs are emerging. Larger and longer prospective studies are required to evaluate the long-term tolerability and safety of these new molecules and assess their real-life advantages and applicability. Future research should focus on the comparison between these and currently available options, to define their role in the treatment of mild-to-moderate psoriasis.

Declarations

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