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PSORIASIS (J WU, SECTION EDITOR)

Topical Therapies for Psoriasis in Phase 3 Trials

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Abstract

Purpose of Review This review will discuss new topical therapeutics for psoriasis that have undergone or published phase III trials in the last 5 years, as well as promising therapeutics in development.

Recent Findings New corticosteroid-only additions to the marketplace include formulations that improve absorption and ease-of-use, including betamethasone dipropionate (BD) 0.05% spray, halobetasol propionate (HP) 0.05% foam and 0.01% lotion, and clobetasol propionate 0.025% cream. Combination therapies include BD 0.064% plus calcipotriene 0.005% (Cal/BD) foam, Cal/BD cream, and HP 0.01% plus tazarotene 0.045% lotion. New treatments are on the horizon, with trials nearing completion for topical phosphodiesterase-4 inhibitors and tapinarof, and trials being planned for turmeric, rose bengal disodium, JAK-inhibitors, and pegcantratinib.

Summary New therapeutic modalities can improve patient satisfaction and adherence, provide better control of disease, and improve quality of life. Thoughtful selection of the appropriate therapy from this growing arsenal will help improve patient care.

Keywords Psoriasis · Treatment regimens · Topical therapy · Clinical trials · Emerging treatments

Introduction

With psoriasis prevalence estimates ranging from 0.51 to 11.43% [1] and at an annual cost of over $112 billion as of 2013 in the USA alone [2], psoriasis remains one of the most common and vexing diseases worldwide. Eighty to 90% of patients suffer from the most common form of the disease, plaque psoriasis, characterized by erythematous and pruritic well-demarcated papules and plaques covered with silvery white scales due to immune dysregulation and subsequent excessive keratinocyte turnover [3]. Although a variety of treatment modalities are available, including topical agents, phototherapy, and systemic treatments, topical therapy alone is first-line in mild and moderate diseases [4], and is prescribed along with systemic agents in more severe cases. In January of 2020, the International Psoriasis Council (IPC) released a consensus statement on the classification of psoriasis severity in which they rejected the prior classification system of psoriasis as mild, moderate, or severe in favor of classifying patients as candidates for topical versus systemic therapy (i.e., biologic, nonbiologic, phototherapy) [5]. Candidates for systemic therapy are those with BSA > 10%, involvement of sensitive areas, or failure of topical therapy [5]. Eighty percent of psoriasis patients are estimated to have localized disease amenable to treatment with topical therapy alone [6]. However, undertreatment remains a significant barrier, with over half of psoriasis patients stating that they are dissatisfied with their treatment [7]. Reasons for dissatisfaction commonly cited by patients include but are not limited to unacceptably high frequency of applications, time-consuming applications, poor cosmetic characteristics, and spread of greasy medication to clothes/bedding [8].

Traditional topical therapies have consisted largely of corticosteroids, vitamin D analogs, retinoids, calcineurin inhibitors, anthralin, and tar available individually as lotions, ointments, creams, gels, or powders. More recently, newer formulations such as foams and sprays have entered the dermatologist's arsenal, as well as additional classes of medication and novel combination therapies (Tables 1 and 2). Through potential improvements in percutaneous absorption and ease of application, these new therapeutic modalities have the ability to improve patient satisfaction and adherence, provide better control of disease, and improve psoriasis-related

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Table 1 Newly FDA-approved topicals for psoriasis over the past 5 years

Therapy	Approval date	Application
Calcipotriene 0.005% plus betamethasone dipropionate 0.064% aerosol foam	October 2015	Once daily to affected area up to 4 weeks in patients ≥ 12 years
Betamethasone dipropionate spray, 0.05%	February 2016	Twice daily to affected area up to 4 weeks for mild-to-moderate disease in patients ≥ 18 years
Clobetasol propionate cream, 0.025%	November 2017	Twice daily to affected area up to 2 weeks for moderate-to-severe disease in patients ≥ 18 years
Halobetasol propionate foam, 0.05%	May 2018	Twice daily to affected area up to 2 weeks in patients ≥ 18 years
Halobetasol propionate 0.01% plus tazarotene 0.045% lotion	April 2019	Once daily to affected area in adults
Calcipotriene 0.005% plus betamethasone dipropionate 0.064% cream	July 2020	Once daily to affected area up to 8 weeks in patients ≥ 18 years

quality of life. Fixed-dose combination therapies also offer the ability to simplify the treatment regimen. Additionally, some vehicle formulations are incompatible when applied simultaneously, yet through enhanced vehicle technology, the same medications can be formulated in a single vehicle can be used in fixed-dose combinations [9].

In this review, we will discuss new strategies for the topical treatment of psoriasis that have undergone phase III trials in the last 5 years, as well as promising therapeutics in development.

Corticosteroid Topicals

While topical corticosteroids have been the mainstay of psoriasis therapy since their initial development in the 1950s, the area of topical steroid monotherapy has seen significant advancement in the last several years, particularly as regards vehicle technology. This push is driven not only by a desire to enhance effectiveness and limit the side effects of longer steroid therapy, but also by dissatisfaction among patients with current topical preparations. Estimates of nonadherence to topical therapies range from 40 to 65% [10–12], driven in part by patient-reported inconvenience of the topical vehicle rather than the therapeutic effect [11]. However, while a new vehicle may offer greater patient choice and potentially increase adherence, it may also alter efficacy, penetration, and side effects. Recently completed trials, including several that led to Food and Drug Administration (FDA) approval, include lotions, sprays, and foam. Sprays and foams provide the advantage of leaving minimal residue and being therefore less messy than more traditional formulations. These vehicles are especially appropriate for hair-bearing areas. The optimal treatment vehicle for individual patients may vary widely, with preferences that are impossible to predict, highlighting the importance of shared decision-making in choosing the optimal therapeutic regimen [13, 14].

Betamethasone

Betamethasone dipropionate (BD) 0.05% is a corticosteroid previously available in superpotent ointment, lotion, and cream formulations. In an attempt to provide an alternative therapeutic vehicle, a BD 0.05% spray has recently been developed, and was approved by the FDA in 2016 for adults with mild-to-moderate plaque psoriasis. Due to decreased systemic absorption as compared to other formulations, BD 0.05% spray has a lower side effect profile and is rated a mid-potency steroid by vasoconstrictive assay. Two randomized, double-blind, placebo-controlled clinical trials tested twice-daily spray for 28 days with a primary endpoint of IGA 0 or 1 and ≥ 2-grade improvement from baseline. Results showed that the BD 0.05% spray was superior to similar applications of vehicle alone for moderate psoriasis by day 15 of treatment, with one study seeing a significant effect as early as day 8 [15]. Another study proved that the

Table 2 Ongoing phase 3 clinical trials of topical therapies for psoriasis

Drug	Company/developer	Status of trial	Date of expected results
Halobetasol propionate 0.05% spray	Therapeutics, Inc.	Completed	2020
Tapinarof 1% cream	Dermavant Sciences	Completed	2020
Roflumilast 0.3% cream	Arcutis Biotherapeutics, Inc.	Recruiting	2021

spray formulation, though mid-potency in rating, was equal in effect to its corresponding superpotent lotion, augmented betamethasone. This study defined treatment success in the same way and randomized 351 patients with moderate psoriasis to BD spray, BD lotion, or vehicle for twice-daily application over 14 days, leading to treatment success in 19.0%, 18.9%, and 2.3% of patients, respectively [16]. Control of symptoms in these studies was rapid, with a subsequent post hoc analysis noting that half of the subjects reported relief of pruritus within 4 days [17].

Halobetasol

Halobetasol propionate (HP) 0.05% is a superpotent corticosteroid previously available in ointment, lotion, and cream formulations. However, new foam and spray formulations have recently been developed. HP 0.05% topical foam was evaluated for the treatment of moderate-to-severe plaque psoriasis in two multicenter, randomized, double-blind, vehicle-controlled studies with a total enrollment of 560 patients. Participants who applied HP 0.05% foam twice daily achieved improvement in pruritis, elevation, scaling, and erythema as well as a IGA of 0 or 1 and at least a two-grade improvement compared to baseline 25.3% and 30.7% of the time, compared to 3.9% and 7.4% in the vehicle arms of the two respective studies [18••]. This foam formulation was subsequently approved by the FDA in 2018 for plaque psoriasis in patients 18 and older. A spray formulation of HP 0.05% has also been tested in two phase III, randomized, double-blind, vehicle-controlled trials involving 423 patients with moderate-to-severe psoriasis, although study results have not yet been released [19, 20].

A new HP lotion at 0.01% concentration was also approved by the FDA in 2018 for the treatment of moderate-to-severe plaque psoriasis based on two successful prospective, multicenter, randomized, double-blind clinical trials [21, 22•]. In these trials, 340 patients applied HP 0.01% lotion or vehicle once daily for 8 weeks, with treatment success defined as at least a 2-grade improvement from baseline in IGA score and an IGA score of "clear" or "almost clear." HP 0.01% lotion outperformed its vehicle, with statistically superior results as early as week 2. By the conclusion of the study, 37% and 38% of treated subjects achieved treatment success, while only 8% and 12% did so when treated with vehicle in each respective trial. No adverse event appeared in more than 1% of subjects.

Clobetasol

While clobetasol propionate (CP) has been available in multiple formulations, including as a 0.05% cream, for many years, recent trials have also demonstrated the efficacy and safety of a 0.025% cream, leading to FDA approval in 2017 for treatment of moderate-to-severe plaque psoriasis. Despite the new cream containing a lower concentration of the active corticosteroid, it retains classification as a superpotent corticosteroid. The new formulation also avoids propylene glycol and sorbitan sesquioleate, the two most common contact allergens found in topical corticosteroids [23•]. In two randomized, double-blind, vehicle-controlled trials involving 543 patients with moderate-to-severe psoriasis, twice-daily applications of CP 0.025% cream for 14 days led to treatment success, as defined by IGA score of 0 or 1 and > 2-grade improvement from baseline, in 30.2% and 30.1% of the treatment arms as compared to 9.0% and 9.7% in the control arms, respectively [23•]. Fewer than 1% of patients who received the active medication experienced telangiectasia, rash, or atrophy. In a maximal use safety study comparing twice-daily use of CP 0.025% cream to use of CP 0.05% cream for 14 days in 45 subjects with moderate-to-severe plaque psoriasis involving 20 to 50% of body surface area (BSA), plasma concentration of CP was significantly less in those patients who used the less concentrated formulation and there was a threefold decrease in hypothalamic-pituitary-adrenal (HPA) axis suppression, though this result did not prove statistically significant [23•]. Efficacy appeared to be similar, at 16.7% in the CP 0.025% group and 18.1% in the CP 0.05% group, though the study was not powered to investigate this outcome.

Vitamin D/Corticosteroid Topicals

The combination of calcipotriene, a vitamin D analogue, and betamethasone dipropionate has been an area of intense exploration in recent years, with phase III clinical trials of foam, suspension, and cream modalities each taking place. As these fixed combinations are used only once daily, they may be preferred by patients and increase adherence to therapy as compared to multiple products. Previously, the combination has been approved by the FDA as both ointment and gel, though these formulations are often messy and difficult to apply for patients with large affected BSA.

Betamethasone/Calcipotriene Foam

A fixed-dose formulation of BD 0.064% and calcipotriene 0.005% (Cal/BD) foam was approved by the FDA in 2015 for plaque psoriasis in patients 18 or older. A randomized, double-blind, multicenter trial showed superiority to foam monads, with 302 patients randomized to once-daily Cal/BD foam, Cal foam, or BD foam for 4 weeks. Forty-five percent of combination-treated patients achieved treatment success, defined as IGA of 0 or 1 with a 2 grade improvement, as compared to 14.9% for Cal foam and 30.7% for BD foam [24].

Another randomized, double-blind, multicenter trial showed increased effectiveness as compared to gel formulation of Cal/BD [25], with 463 patients randomized for once-

daily treatment with either combination gel, combination foam, gel vehicle, or foam vehicle. A significantly greater proportion of those treated with combination foam achieved treatment success, defined as clear/almost clear with a ≥ 2 grade IGA improvement at week 4 for Cal/BD foam versus week 8 for Cal/BD gel, than those treated with gel (38% versus 22%) [25]. A separate study randomized patients with mild-to-severe psoriasis to once-daily Cal/BD foam for 1 week, followed by Cal/BD gel for 1 week, or vice versa, polling them throughout regarding their preferences for and satisfaction with the two formulations. Although patients did express strong preferences for each treatment, 50% preferred Cal/BD foam and 50% preferred Cal/BD gel. Both forms were significantly more preferred than the patient's latest topical treatment, particularly if that topical treatment had been an ointment or cream [26]. These results highlight the importance of patient preferences regarding modality and the availability of a variety of options in choosing the optimal topical formulation for psoriasis treatment.

Completing the comparison to available formulations, a randomized, investigator-blind trial involving 376 patients showed greater treatment success, defined as IGA of 0 or 1 with at least a two-step improvement, with Cal/BD foam versus Cal/BD ointment (54.6% versus 43%) [27]. A subsequently pooled analysis of multiple published trials of Cal/BD foam including 1104 patients from 3 separate randomized, double-blind trials confirmed superiority to ointment, gel, monads, and corresponding vehicles [28••]. The success of the new foam formulation is likely due to the increased bioavailability and hence enhanced penetration of the foam compound as compared to other formulations such as ointment [29, 30].

Betamethasone/calcipotriene foam had a label extension in 2019 to children as young as 12 based on positive results from a phase II clinical trial [31•]. This open-label, non-controlled, single-group, 4-week trial included 106 patients with at least mild plaque psoriasis and resulted in treatment success on the body and scalp in 71.8% and 75.7%, respectively, by the study endpoint. Although 32 treatment emergent adverse events (TEAE) occurred, none led to study withdrawal, and all except two were classified as mild. Systemic exposure to Cal/BD was minimal, and there was no evidence of dysregulation in tests of the HPA axis.

A phase III study comparing generic Cal/BD foam to the marketed formulation is currently recruiting [32].

Betamethasone/Calcipotriene Cream

Recently, a proprietary cream vehicle containing a fixed-dose Cal/BD 0.005%/0.064%, also known as MC2-01, completed two phase III clinical trials involving 796 patients randomized to MC2-01, Cal/BD topical suspension, and MC2-01 vehicle daily for 8 weeks. Treatment success was measured as a 2-point improvement from baseline in IGA score, with success by week 8 at 40.1%, 24.0%, and 4.5%, respectively [33]. MC2-01 also led to a significant decrease in pruritus as compared to vehicle on an 11-point itch severity scale, and measurements of modified psoriasis area and severity index score (mPASI) from baseline indicated that MC2-01 cream was superior to Taclonex suspension at every week of treatment. Though no mechanistic data has been published, the manufacturer claims that a decreased amount of surfactant in a unique oil-in-water dispersion helps lead to decreased irritation and superior medication delivery [34]. MC2-01 cream was approved in 2020 by the FDA for the treatment of plaque psoriasis in adults based on these trial results.

Retinoid/Steroid Topicals

Another exciting new development in topical therapy has been the FDA approval of a fixed-dose halobetasol propionate 0.01% plus tazarotene 0.045% (HP/Taz) lotion in 2019. Tazarotene has long been known to exhibit a complimentary effect with topical steroids in the treatment of psoriasis, optimizing their efficacy while minimizing safety and tolerability concerns [35, 36]. A 212-patient phase II study of daily treatment in those with moderate-to-severe psoriasis showed superiority to vehicle or either individual topical component at week 8 of treatment [37]. Treatment success, as defined by a 2-grade improvement in IGA or a score of "clear" or "almost clear," was seen in 52.5% of patients in the combination therapy arm, 33.3% in the HP-only arm, 18.6% in the tazarotene-only arm, and 9.7% in those treated with vehicle alone.

Of 418 patients with moderate-to-severe psoriasis enrolled in two randomized, double-blind, vehicle-controlled phase III trials, those treated with HP/Taz showed significantly reduced disease severity after 8 weeks of daily application. Treatment success was defined as ≥ 2-grade IGA score improvement and a score of "clear" or "almost clear" skin, with success in 35.8% and 45.3% in the two treatment arms, as compared to 7.0% and 12.5% in the vehicle arms, respectively [38•]. Those treated with HP/Taz also maintained their treatment success over the ensuing 4-week post-treatment period (33% versus 9% in vehicle-treated, both studies combined).

While treatment with potent steroids such as BD is often limited to 2 to 4 weeks due to concern for adverse effects, a phase III, multicenter, open-label yearlong safety trial was conducted. Daily HP/Taz lotion was used as needed in 4-week intervals for up to 1 year in 555 subjects with moderate psoriasis. Efficacy was sustained throughout the trial, while adverse events were comparable to that reported in studies of the typical, shorter courses of treatment [39••]. Adverse events consisted chiefly of pruritus, dermatitis, and pain. Subjects were evaluated every 4 weeks, and treatment was held in those who had reached treatment success, defined as IGA of 0 or 1. Patients resumed drug if their IGA was > 2. Patients who did

not achieve treatment success by the end of 24 consecutive weeks of treatment were discontinued from the study. One-fifth of subjects did not achieve success by the 24-week point, while 7.5% of subjects discontinued treatment due to adverse effects. This combination therapy applied only once daily and with the ability to be used over extended periods of time has the potential to significantly improve patient adherence, a key barrier to the success of topical treatments.

Phosphodiesterase-4 Inhibitor Topicals

Phosphodiesterase-4 (PDE-4) is an intracellular enzyme involved in inflammation and epithelial integrity via modulation of cyclic adenosine monophosphate levels in immune, epithelial, and brain cells [40]. Oral PDE-4, apremilast, is approved for treatment of psoriasis. The increased safety profile [41] as compared to the known side effects of high-potency topical steroids also makes PDE-4 inhibitors attractive candidates for both long-term therapy and the treatment of pediatric patients. Though topical treatment with the PDE-4 inhibitor crisaborole has been FDA-approved for atopic dermatitis, it failed to outperform its vehicle in a 68-patient vehicle-controlled phase II trial in patients with mild-to-moderate psoriasis, and no phase III studies are underway [42].

However, trials are in progress involving other topical PDE-4 inhibitors for psoriasis, such as the long-acting PDE-4 inhibitor roflumilast, which showed positive results in phase IIa and IIb trials. A recently published 331-patient phase IIb trial compared roflumilast 0.3% cream, roflumilast 0.15% cream, or vehicle cream once daily for 12 weeks, finding that 28%, 23%, and 8% of patients achieved an IGA of clear or almost clear by week 6 in each group, respectively [43••]. No formal comparisons were made between dose levels, but two identical 400-participant phase III trials are studying daily application of 0.3% topical roflumilast cream or vehicle cream over 8 weeks [44, 45]. An open-label extension will study daily application for an ensuing 24 weeks in 250 patients to assess long-term safety and efficacy [46]. Notably, each of these trials has been able to include patients as young as 2 years due to roflumilast's exceptional safety profile. Multiple phase III trials have also been completed with pefcalcitol, a topical PDE-4 inhibitor combined with a vitamin D derivative [47–50]. However, no phase III results have yet been reported.

Tapinarof

Tapinarof is a first-in-class proprietary nonsteroidal small molecule that acts as an anti-inflammatory compound via the aryl hydrocarbon receptor, which itself controls expression of multiple cytokines involved in the pathogenesis of psoriasis such as IL-10, IL-17A, IL-21, and IL-22 [51]. This mechanism is similar to that postulated to underly the efficacy of coal tar [52]. A randomized, double-blind phase II trial of tapinarof cream proved encouraging, showing statistically improved control of psoriasis across 2 doses (0.5% and 1%) and 2 treatment frequencies (once and twice daily) as defined by IGA 0 or 1 and a 2-grade improvement by week 12 [53•]. These gains were also maintained at 4 weeks post-trial. Once-daily tapinarof 1% cream is now being studied in two identical randomized, placebo-controlled, 12-week phase III trials with a total of 1025 participants with mild-to-severe psoriasis, and a long-term extension for an additional 44 weeks is ongoing in 477 participants [54–56]. Data is expected at the end of 2020.

New Therapeutics on the Horizon

There are several promising topical therapies that have shown promise in phase II trials and may be moving into phase III trials in the near future, including turmeric, rose bengal disodium, JAK-inhibitors, and pegcantratinib. Turmeric (curcumin), a selective phosphorylase kinase inhibitor, has been shown in one small randomized, intra-individual, right-left comparative, placebo-controlled, double-blind clinical trial to lead to statistically significant decreases in scaling, erythema, and plaque thickness [57], and in another small trial to lead to improvement in patients with chronic disease resistant to steroids, methotrexate, and calcipotriol [58]. A phase III trial of topical turmeric therapy is currently planned but not yet recruiting [59]. Rose bengal disodium, also known as PH-10, is a small molecule compound originally developed as an ophthalmic stain that is currently under investigation in a topical hydrogel form for the treatment of plaque psoriasis. A mechanism-of-action study found that the compound down-regulated > 500 psoriasis-related genes, effectively normalizing lesional skin values [60]. While the manufacturer has announced promising phase II trial results, including complete or nearly complete resolution of erythema, induration and desquamation in 23–29% of subjects treated in a 99-patient study [61], no phase III trials have yet been announced. Janus kinase (JAK) inhibitors block several inflammatory cytokine pathways thought to be critical to psoriasis. Oral and topical formulations are being evaluated for psoriasis. However, while topical JAK-inhibitors including ruxolitinib and tofacitinib have been studied repeatedly in phase II trials, showing modest efficacy [62–67], none have moved into phase III trials or been approved by the FDA for the treatment of psoriasis. Pegcantratinib, also known as SNA-120, is a first-in-class topical inhibitor of tropomyosin receptor kinase A (TrkA) in neurons that was designed to modulate the intense pain, burning, and pruritus of psoriatic lesions. In a placebo-controlled phase II trial of twice-daily treatment in 208 patients with mild-to-moderate psoriasis, 29% of patients

achieved a 2-grade improvement in IGA and clear or almost clear skin, as compared to 13% of those treated with vehicle alone [68]. Patients also showed improvements in pain and burning over placebo, but not pruritus. In 2019, the manufacturer announced an intention to move to phase III trials, though the company has since filed for bankruptcy protection [69], and no trial has been announced or registered, leaving the future of this treatment modality in some question.

Conclusion

The past 5 years have seen extensive innovation in topical therapeutics for psoriasis. New formulations of therapies with proven mechanisms have entered the marketplace, including enhanced vehicles that may improve penetration and prove more palatable for patients, hence improving adherence and therapeutic effect. New combination formulations of both tazarotene and calcipotriene with topical steroids now allow for complimentary effects in an easy-to-apply fixed combination, which may decrease patient frustration with complicated or burdensome topical regimens. At the same time, topical agents with novel mechanisms are moving towards the market, including topical tapinarof, PDE-4 inhibitors, and JAK-inhibitors. Thoughtful selection of the appropriate therapy from this enlarging arsenal should allow improved patient care, and additional forthcoming trial data should lead to even further options for personalization of patient regimens.

Compliance with Ethical Standards

Conflict of Interest Mr. Buechler and Dr. Veenstra have nothing to disclose. Dr. Stein Gold reports grants and personal fees from Leo Pharma, Arcutis, Incyte, Ortho Derm, Pfizer, Dermavant, and Sun during the conduct of the study.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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