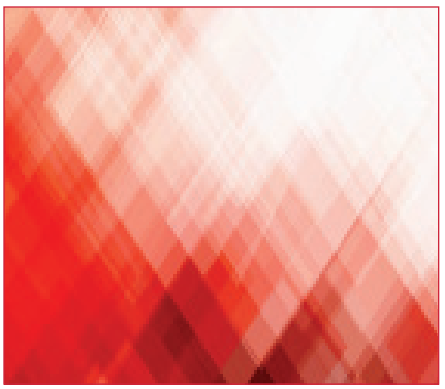

REVIEW

New and Emerging Topical Therapies for Psoriasis and Atopic Dermatitis

ABSTRACT

Psoriasis and atopic dermatitis represent two of the most common skin conditions seen by both primary care and specialist dermatology. The prevalence of psoriasis in North America is 2 to 4 percent, and it is estimated to cost more than $3 billion per year to treat this condition. Atopic dermatitis has an estimated 15 to 30 percent lifetime prevalence in children and an 8 to 10 percent lifetime prevalence in adults. Both diseases have a significant impact on patient quality of life, as well as associated psychological, social, and economic consequences. While systemic therapies are available for both, the majority of patients with each condition are treated with topical therapies alone, with varying degrees of efficacy and patient satisfaction. As such, there is both need and an incentive to develop new treatments for these two conditions. In this paper, we review new and emerging topical therapies for psoriasis and atopic dermatitis.

KEYWORDS: Psoriasis, atopic dermatitis, eczema, topical, steroid, vitamin D analog, enstilar, sernivo, hydroxypropyl-chitosan, Crisaborole, Eucrisa, phosphodiesterase-4 inhibitor, PDE4 inhibitor, JAK-STAT, JAK inhibitor, Pefcalcitol, Tofacitinib, Genador, tazarotene, Benvitimod, retinoids, PH-10, GATA-3

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Psoriasis and atopic dermatitis represent two of the most common skin conditions presenting to both primary care and specialist dermatology. The prevalence of psoriasis in North America is 2 to 4 percent, and it is estimated to cost more $3 billion per year to treat this condition.[1–4] Psoriasis has a significant impact on patient quality of life. In addition to its psychological, social, and economic consequences, it is associated with a number of chronic health conditions, including metabolic syndrome, diabetes, and cardiovascular disease.[1,2,4,5] Atopic dermatitis has an estimated 15-to-30-percent lifetime prevalence in children and 8-to-10-percent lifetime prevalence in adults—rates that are increasing.[6–8] As with psoriasis, atopic dermatitis can create a significant burden on a patient's life, affecting his or her self-esteem, sleep, school performance, and career.[7] While systemic therapies are available for both, the majority of patients with each condition are treated using topical therapies alone, with varying degrees of efficacy and patient satisfaction. As such, there is both a need and an incentive to develop new treatments for these two conditions. In this paper, we review new and emerging topical therapies for psoriasis and atopic dermatitis.

PSORIASIS

Plaque psoriasis is a chronic, immune-mediated skin disease characterized by the dysregulation of keratinocytes and presenting as red, scaly plaques on the skin. Activated T-helper cells (especially Th17) and multiple cytokines, including interleukin (IL)-10. IL-17, IL-22, IL-23, and tumor necrosis factor alpha (TNF-α) are implicated in the pathogenesis of the disease.[9–11] The majority of patients with psoriasis experience mild-to-moderate severity and are successfully managed with topical therapies alone.[5,12] The most widely used topical medications for psoriasis include vitamin D analogs, corticosteroids, and retinoids. With a few exceptions, the new medications under development tend to be either new formulations or novel combinations of these existing therapies. In the case of modifications of existing therapies, improvements have been made in the areas of delivering a more sustained dose of medication and improving patient tolerability, especially for individuals who are not satisfied with the experience of greasy, occlusive ointments.[4]

Vitamin D analogs and corticosteroids.

Topical vitamin D3 analogs and corticosteroids have been mainstays of psoriasis treatment for many years. The precise mechanism of action of vitamin D3 analogs is not exactly understood; however, they have been shown to inhibit growth and induce differentiation of keratinocytes.[9,13–15] Topical steroids have broad anti-inflammatory and immunosuppressive effects.[9,16]

Existing formulations that combine a vitamin D3 analog with the corticosteroid betamethasone diproprionate (BD) have demonstrated superior efficacy over that of either product alone.[4,5,17,18] A novel combination of calcipotriol (Cal) 0.005% with BD 0.064%

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in a foam vehicle was introduced in 2015. The foam vehicle delivers a supersaturated solution of its active ingredients, allowing for greater penetration and bioavailability of both the Cal and BD.[19] The product acts by inhibiting keratinocyte proliferation, promoting epidermal differentiation, and decreasing the rate of mitosis in the epidermis. It also acts as an anti-inflammatory by reducing pro-inflammatory cytokines including IL-8, IL-17A, IL-22, and TNF-α *in vitro*.[12]

In randomized, multicenter trials, up to 54.6 percent of patients using Cal/BD foam once daily showed marked improvement in disease as assessed by the Physican Global Assessment of Disease Severity (PGA) scale at the end of four weeks, with over half achieving treatment success (defined as "clear" or "almost clear").[4,5,12,20] A pooled analysis of three clinical trials compared the efficacy of Cal/BD foam to Cal/BD ointment, BD aerosol foam, Cal aerosol foam, aerosol foam vehicle, and ointment vehicle.[5] In total, 1,104 patients were included, 1,051 of whom completed the full study. Participants were aged 18 years or older with mild-to-severe disease according to the five-point PGA scale, had 2-to-30-percent body surface area (BSA) involvement, and a modified Psoriasis Area and Severity Index (mPASI) score of at least two points. All randomized patients were included in the analysis, and missing data were addressed using the last observation carried forward (LOCF) method.

A total of 564 patients were included in the Cal/BD aerosol foam group; their median age was 51 (18–87) years. The mean BSA affected was 7.3±6.3 percent. In this analysis, 51.4 percent of patients using Cal/BD aerosol foam achieved treatment success (as defined above), a number significantly greater than that in any of the other groups receiving either individual component as a foam (Cal: 14.9% or BD: 30.7%), a foam vehicle (5.3%), a combined ointment (43%), and ointment vehicle (7.8%).[5,12]

Furthermore, patients using the Cal/BD foam formulation reported high satisfaction with symptom improvement, the speed with which it took effect, and the feeling of the product.[20] In addition to improved efficacy and satisfaction, the new combination foam has cost implications, with one study estimating up to US $36 million could be saved by using Cal/BD foam as part of a stepwise management approach alongside biologics in a subset of patients with moderate-to-severe plaque psoriasis.[21] The model compared the cost of one scenario, based on recent market data of the cost to treat moderate-to-severe psoriasis in patients who are candidates for biologics, to an alternate scenario in which 20 percent of patients on biologics would use topical Cal/BD. In their conclusion, the authors suggested Cal/BD foam could be used as a cost-saving initial treatment step in patients with moderate-to-severe plaque psoriasis who are good candidates for topical treatment (i.e., not those with psoriatic arthritis or features clearly warranting the use of systemic therapy).

A novel 0.05% BD emollient spray was approved by the United States Food and Drug Administration (FDA) in 2016 for the treatment of mild-to-moderate plaque psoriasis in adults older than 18 years. This new formulation was designed to optimize the concentration of its active ingredient, improve penetration into the epidermis, and limit systemic absorption of the steroid. The BD spray is rated as a mid-potency (Class 3) steroid per the vasoconstriction assay test but has the clinical activity of a superpotent (Class I) steroid per clinical study results.[22,23]

Two Phase III studies, including a total of 538 subjects (94.4% completed the trial), were carried out comparing BD emollient spray to vehicle randomized in a 2:1 fashion; a separate Phase III trial of 351 subjects (95.4% completed the trial) compared such to a superpotent steroid and vehicle (randomized as 2:1:1). Patients in the clinical trials had 10-to-20 percent BSA involvement, with a mean BSA involvement of 13 to 14 percent, on areas excluding the face, scalp, and intertriginous areas. All topicals in the trials were applied twice daily for two weeks. The BD spray demonstrated statistically significant superiority to vehicle and similar efficacy to that of the superpotent steroid (BD spray: 19%; superpotent steroid: 18.9%).[22] In the trial comparing BD spray to vehicle, 20 percent of subjects achieved success with spray versus five percent with vehicle ($p<0.001$) at Day 15, while 38.7 percent versus 12.6 percent achieved success at Day 29 ($p<0.001$).[23] Treatment success was defined as an Investigator Global Assessment (IGA) score of zero or one point(s), and two-grade-or-greater improvement from the baseline score. The novel formulation achieved greater reduction in erythema and scale by Day 4, and statistically less burning and stinging were reported than with the super potent steroid (4.1% vs. 13.6%; $p=0.010$).[22]

Nail psoriasis can be very challenging to treat, and there is no dedicated treatment exclusively targeting this entity. The vitamin D analog calcipotriene is being investigated as a 0.005% nail solution (P-3073) to treat nail psoriasis. A randomized, double-blind, vehicle-controlled, parallel-group Phase II trial was completed, comparing the use of calcipotriene 0.005%, cyclosporine 5%, and vehicle applied once daily for 24 weeks, with patients followed for 12 weeks.[24] Patients between the ages of 18 and 80 years with mild-to-moderate psoriasis (BSA≤10% or PASI score≤10 points) with fingernail psoriasis of the nail matrix and/or nail bed were randomized 2:2:1 to treatment and placebo groups. A full analysis was conducted involving 30 patients from the cyclosporine group, 34 patients from the calcipotriene group, and 14 in the vehicle-only group (the authors did not specify how many people were enrolled in the study). The primary endpoint was the total Nail Psoriasis Severity Index (NAPSI) score at the end of treatment. Calcipotriene 0.005% nail solution significantly reduced the total NAPSI score (−6.78) compared to vehicle (−1.11) ($p=0.0395$), as well as reduced NAPSI of both the nail bed and nail matrix. The superiority of calcipotriene 0.005% was apparent by Week 12 of treatment and sustained throughout the study. A Phase III trial is underway.[25]

Hydroxypropyl–chitosan (HPCH) nail lacquer. A water-soluble nail lacquer containing HPCH, horsetail extract (*Equisetum arvense*), and methylsulphonylmethane might be effective in reducing signs of psoriatic nail disease. One study investigated 30 adult patients aged 18 to 75 years with mild-to-moderate nail psoriasis of the matrix and/or nail bed (baseline NAPSI score: 2.83±0.99 points) who applied the lacquer to the fingernails of their left hand once daily for 24 consecutive weeks. Twenty-eight patients were included in the analysis (two were lost to follow-up) and, from baseline to end of treatment, there was a 72-percent reduction in pitting, 66-percent reduction in leukonychia, 63-percent reduction in onycholysis, and 65-percent reduction in NAPSI score in the treated nails.[26] There were no changes in the nails of the right hand.

Another randomized, controlled trial with 87 patients aged 16 to 80 years with mild-to-

moderate nail psoriasis of the nail matrix and/or nail bed in at least one fingernail found the HPCH lacquer to be significantly superior to placebo after nightly application to all fingernails for 24 weeks. The LOCF method was used for patients who prematurely withdrew from the study. Eighty-one patients were included in the intention-to-treat (ITT) analysis; of those, 55 percent (22/40) of patients who applied the lacquer were clinically cured after 24 weeks versus 31.7 percent (13/41) of patients who applied the placebo (p=0.045).[27]

Phosphodiesterase-4 (PDE-4) inhibitors. Crisaborole is a topical PDE-4 inhibitor that is FDA-approved to treat mild-to-moderate atopic dermatitis and is discussed in further detail below. Clinical trials investigating its use as a topical treatment for psoriasis have been completed, but its development was halted and no published studies have reported its efficacy to date.[28] Pefcalcitol, a topical PDE-4 inhibitor combined with a vitamin D derivative, is currently in Phase III clinical trials in the United States and Europe and Phase II trials in Japan.[29,30]

There is evidence that oral PDE-4 inhibitors are successful in treating psoriasis, and their mechanism of action—inhibiting the breakdown of cyclic adenosine monophosphate (cAMP)—decreases the presence of proinflammatory cytokines that are known to be involved in the pathogenesis of psoriasis.[31–33] There is one published article that reports success in treating two patients with psoriasis using crisaborole ointment.[34] While the data are limited, topical PDE-4 inhibitors could show promise for treating psoriasis and are worth looking out for in the future.

Topical Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitors. The JAK–STAT pathway has been implicated in the pathogenesis of several inflammatory skin diseases, including psoriasis and atopic dermatitis, and has proven to be a useful therapeutic target.[35,36] Activation of the JAK–STAT pathway leads to T-cell activation; Th17 differentiation; and increased levels of IL-10, IL-22, and IL-23 among others.[36] JAK inhibitors have shown some efficacy in treating psoriasis as both oral and topical formulations.[37]

A randomized, double-blind, vehicle-controlled Phase IIb study of topical tofacitinib, a JAK inhibitor, was conducted across 52 centers in four countries. In total, 435 subjects aged 18 to 85 years with mild (score of two points) or moderate (score of three points) plaque psoriasis, graded using the Calculated PGA (PGA-C) scale were randomized 1:1:1 to receive topical tofacitinib 1%, 2%, or vehicle in once-daily and twice-daily groups. Participants were required to have 2-to-20-percent BSA involvement of the trunk and/or limbs. The study's primary endpoint was a PGA-C outcome of "clear" or "almost clear" and two-grade-or-more improvement from baseline at Weeks 8 and 12. This was an estimation study, including a sample of 70 patients from each treatment group; those included were randomized and received at least one treatment dose. The authors found significantly higher improvement was achieved with all tofacitinib regimens versus vehicle at Week 8, while no difference was seen at Week 12.[38] However, their secondary endpoint—the proportion of patients achieving a PGA-C result of "clear" or "almost clear"—was significantly higher for the tofacitinib 2% twice-daily regimen at Week 12. The investigators also found that patients experienced reduced pruritus. Further studies are needed to establish the true efficacy of JAK inhibitors as well as the appropriate dose to use. There is additionally some potential for developing medications that act on the STAT component of the pathway, as STAT3 is known to be activated in psoriatic lesions.[39]

Combination retinoid and corticosteroid lotion. Topical retinoids are an effective monotherapy for psoriasis. Tazarotene acts to reduce keratinocyte differentiation and proliferation as well as inflammation.[40] Past studies have demonstrated a synergistic effect when tazarotene is combined with a medium- or high-potency steroid.[40,41] An initial Phase II clinical trial investigating halobetasol propionate 0.01% plus tazarotene 0.045% (HP/TAZ) lotion once daily for eight weeks in moderate-to-severe plaque psoriasis demonstrated statistically significant superiority over monads and vehicle as early as two weeks from treatment onset.[42] At eight weeks, 67.7 percent of patients applying HP/TAZ achieved the primary efficacy outcome of at least a two-grade improvement from baseline IGA score and a score of "clear" or "almost clear" at four weeks after treatment in comparison with 61.9 percent (p=0.042) of those treated with HP and 54.5 percent (p=0.004) of those treated with TAZ alone. Participants were adults older than 18 years with IGA scores of three or four points and an affected BSA of 3 to 12 percent (mean: 5%). In total, 212 patients were randomized to the treatment groups, and all were included in the ITT analysis using LOCF method for missing data.

A recent review of two Phase III trials also found a statistically significant difference between HP/TAZ and vehicle. At Week 8 of treatment, 35.8 percent (Study 1) and 45.3 percent (Study 2) of patients receiving the HP/TAZ combination achieved the primary endpoint (IGA score of "clear" or "almost clear" plus at least a 2-grade improvement from baseline IGA score) as compared to 7.0% (Study 1) and 12.5 percent (Study 2) of those applying the vehicle.[43] Furthermore, HP/TAZ lotion more effectively reduced erythema, plaque elevation, and scaling of lesions.[42,43] The initial application for the FDA approval of HP/TAZ lotion was rejected in June 2018 due to questions regarding pharmacokinetic data, per the manufacturer.[44] At the time of writing, the reapplication is still pending FDA approval.

PH-10. PH-10 is a topical hydrogel formulation of rose bengal disodium. Rose bengal disodium is under investigation for multiple uses, including melanoma. The chemical compound was initially developed as a stain used for ophthalmologic purposes. A total of 226 adult patients with mild-to-moderate plaque psoriasis per PASI on the trunk and extremities was treated with PH-10 in Phase I and Phase II clinical trials. Patients applied PH-10 to plaques daily for 28 days.[45–47] Per the manufacturer, their Phase IIc clinical trial was completed, and the results showed the lowest concentration tested (0.002% vs. 0.005% and 0.01%) had the best therapeutic activity.[48] The manufacturer reported results of a study in which biopsies were taken from patients who applied the formulation to psoriatic lesions and compared to those who applied the vehicle. PH-10 treatment resulted in the downregulation of more than 500 genes relating to psoriasis and demonstrated reduced levels of IL-17, IL-22, and IL-23, among others.[49] The exact mechanism of action was not reported.

Tapinarof. Tapinarof (2-isopropyl-5-[(E)-2-phenylethenyl]benzene-1,3-diol) is a proprietary nonsteroidal small molecule that acts as an anti-inflammatory compound in the treatment of plaque psoriasis. It is naturally derived from bacteria symbiotic to certain nematodes. Tapinarof acts on

the aryl hydrocarbon receptor (AhR), a transcription factor widely expressed in skin that regulates innate and adaptive immune responses, affecting Th17 and regulatory T-cells. The compound also plays a role in the development and maintenance of the skin barrier, upregulating the barrier genes filaggrin, hornerin, and involucrin in human keratinocytes.[50] Tapinarof has been shown to inhibit the activation and migration of T-cells and to decrease multiple pro-inflammatory cytokines including TNF-α, IL-2, IL-13, IL-17A, and interferon gamma.[27,50–52]

A randomized, double-blinded, Phase IIa study compared the efficacy of 1% tapinarof (previously WBI-1001 or Benvitimod) cream versus placebo applied twice daily for 12 weeks. Sixty-one participants aged 18 to 65 years (mean: 50.6 years) with 1-to-10-percent BSA involvement (excluding the face, scalp, and intertriginous areas) and PGA scores of two (mild) to four (severe) points were included in the ITT analysis using LOCF for missing data. The primary efficacy outcome was PGA score judging overall lesion severity at Day 84. Ultimately, 67.5 percent of the WBI-1001 group achieved a PGA score of "clear" or "almost clear" at Day 84 compared to 4.8 percent in the placebo group ($p<0.0001$).[51] A Phase III trial was recently completed at Peking University People's Hospital in Beijing, China, comparing 1% tapinarof to 0.005% Cal ointment and placebo. The results have not yet been published.

ATOPIC DERMATITIS

Atopic dermatitis is a common, chronic inflammatory skin condition characterized by disrupted skin barrier function and immunoglobulin E sensitization to environmental allergens. The mainstays of atopic dermatitis treatment are over-the-counter emollient creams that preserve the skin's barrier function, and anti-inflammatories, such as topical corticosteroids, PDE-4 inhibitors, and topical calcineurin inhibitors. The high prevalence of atopic dermatitis and concerns with side effects of long-term corticosteroid use—for example, skin thinning, striae, telangiectasias, delayed wound healing, and increased susceptibility to or the exacerbation of infections (e.g., candidiasis, tinea incognito)[53]—warrant the development of new treatment options. Novel emerging topical therapies for atopic dermatitis overlap with those under development for psoriasis and include selective PDE-4 inhibitors, JAK inhibitors, and the small molecule benvitimod, among others.

Selective PDE-4 inhibitors. PDEs are a family of enzymes, and PDE-4, whose function is to degrade cAMP, is the predominant enzyme found in immune cells.[54,55] PDE-4 has been found to inhibit cAMP breakdown, which suppresses the release of TNF-α, interferon gamma, IL-17, IL-23, IL-4, IL-5, IL-13, and IL-22, all of which are cytokines implicated in the pathogenesis of atopic dermatitis.[56]

Crisaborole is a benzoxaborole PDE-4 inhibitor, which is a new class of topical medication recently FDA-approved to treat mild-to-moderate atopic dermatitis in patients older than two years of age. Crisaborole utilizes a novel boron base whose structure more effectively inhibits cAMP breakdown.[57] The boron atom binds with bimetal ions in the catalytic site of PDE-4, thereby inhibiting its breakdown. In a study of two randomized double-blinded trials comparing crisaborole ointment to vehicle (ratio of 2:1), crisaborole applied to lesions twice daily for 28 days demonstrated significant efficacy, with 51.7 percent of patients achieving an Investigator's Static Global Assessment (ISGA) result of "clear" or "almost clear" on Day 29 (vs. 40.6% who applied vehicle; $p=0.005$) in one trial and 48.5 percent (vs. 29.7% with vehicle; $p<0.001$) in the other.[58] Participants in this study were two to 79 years of age (mean: 12 years) with a clinical diagnosis of atopic dermatitis, five-percent-or-more BSA involvement (mean: 18%), and a baseline ISGA score of mild (two points) or moderate (three points) dermatitis. All patients in the ITT population, who were randomly assigned to treatment groups and who received the medication, were included (503:256 and 513:250, respectively, for crisaborole:vehicle) in the analysis.

To date, at least seven trials have been carried out evaluating crisaborole, which largely suggest the 2% preparation is ideal and indicate the medication is highly effective against pruritus.[59] There has also been criticism of the medication's true efficacy and degree of benefit, with continued calls for trials that compare crisaborole to standard-of-care therapy versus vehicle preparations.[60]

OPA-15406, another novel PDE-4 inhibitor, demonstrated efficacy in a Phase II trial. Application of 1% OPA-15406 twice daily for eight weeks showed significant improvement in baseline Eczema Area and Severity Index (EASI) scores as well as a reduction in pruritus when compared with vehicle.[61]

Similarly, other trials suggested the novel E6005 PDE-4 inhibitor was efficacious in adults treated with 0.1% and 0.2% E6005 ointment compared to vehicle. There was a concentration-dependent drop in target lesion severity score, which was significant in the highest dose (mean percent change: -54.3% in the 0.2% group).[62] Additionally, EASI and Severity Scoring of Atopic Dermatitis (SCORAD) scores significantly decreased at Week 12 (at Week 4, they had decreased but not significantly).[62,63] Promising results were also published from a study investigating E6005 ointment use in children aged two to 15 years with mild-to-moderate atopic dermatitis, who showed promising but not statistically significant improvements.[64]

JAK inhibitors. Tofacitinib, the small-molecule JAK inhibitor also studied for psoriasis, blocks the proinflammatory JAK–STAT pathway discussed above and suppresses the release of various cytokines implicated in atopic dermatitis pathogenesis. A four-week, Phase IIa, randomized, double-blind, vehicle-controlled study of 69 adults aged 18 to 60 years with mild (PGA score of two points)-to-moderate (PGA score of three points) atopic dermatitis covering 2 to 20 percent BSA compared twice-daily therapy to 2% tofacitinib ointment to vehicle ointment. The primary outcome measured was a percentage change in EASI score from baseline at four weeks. At the end of four weeks, EASI score in the tofacitinib group was reduced by 81.7 percent versus 29.9 percent in the vehicle group, and 73 percent of tofacitinib users had a PGA score of "clear" or "almost clear" versus 22 percent in the vehicle group.[65] The study was not conducted for statistical comparison. Despite its possible preliminary success, trials for tofacitinib have not progressed past Phase II.[66] Other novel JAK inhibitors, such as JTE-052, are in the pipeline, with several clinical trials underway.[66,67]

GATA-3 deoxyribozymes (DNAzymes). GATA-3 is a transcription factor involved in the regulation of Th2 immune responses. More specifically, it drives the differentiation and activation of Th2 cells and induces the release of cytokines involved in the pathogenesis of atopic dermatitis.[68–70] Furthermore, GATA-3 activates a

positive-feedback loop that leads to increased GATA-3 and Th2 differentiation.[68] SB011 is an investigational product whose topical formulation contains 2% hgd40, a DNAzyme that targets GATA-3 and cleaves its messenger RNA. DNAzymes are artificially synthesized DNA oligonucleotides capable of performing certain chemical reactions. A Phase II clinical trial of 25 adults aged 18 to 69 years was completed in January 2017. Results of the study have not yet been published.[69]

Tapinarof. The same novel compound tapinarof (2-isopropyl-5-[(E)-2-phenylethyl] benzene-1,3- diol) that is being developed as a psoriasis treatment has also shown promise as an atopic dermatitis treatment in a clinical trial. A total of 148 patients aged 18 to 65 years with 3-to-20-percent BSA involvement and IGA scores of two to four (mild to severe) points were randomized to receive 0.5% tapinarof cream, 1% tapinarof cream, or placebo twice daily for six weeks. All patients were included in the ITT group and missing data were not estimated. At the end of the trial period, patients in the 1% treatment group showed the greatest decrease in IGA score (56.3%), followed by those in the 0.5% group (43%) and placebo (14.7%).[71] The tapinarof 1% group also had the greatest improvement in EASI, SCORAD, and pruritus scores.

DISCUSSION

Psoriasis and atopic dermatitis are often successfully managed by medications that have been on the market for decades. However, many cases can present therapeutic challenges, with patients failing multiple lines of treatment. Given the frustrating and profound effect each disease can have on patients, it is imperative to develop steroid-sparing treatment alternatives, both for patients who cannot tolerate current treatments and for those who are not satisfied with their outcomes.

In the realm of topical therapies, the new options discussed in this paper, particularly the novel combinations of existing therapies, JAK–STAT inhibitors, and PDE-4 inhibitors, show promise for treating each condition. These topicals might prove to be effective as stand-alone treatments or might be beneficial as an interim treatment step before initiating systemic therapy. While topical therapy alone might be preferable or adequate in some patients, there are subsets who will not achieve treatment success with topicals alone and whose disease presentation makes them optimal candidates for systemic therapy, such as those with joint involvement, evidence of treatment failure with topicals, or a significant psychosocial impact.

As we gain insight into the underlying mechanisms of each disease and the cytokines involved in their pathogenesis, attractive new therapeutic targets will reveal themselves. It is the responsibility of dermatologists to stay abreast of these new treatments, which could dramatically improve the quality of life of their patients.

REFERENCES

1. Boehncke WH, Schön MP. Psoriasis. *Lancet.* 2015;386(9997):983–994.
2. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol.* 1999;41(3 Pt 1):401–407.
3. Gudjonsson JE, Elder JT. Psoriasis: epidemiology. *Clin Dermatol.* 2007;25(6):535–546.
4. Taraska V, Tuppal R, Olesen M, et al. A novel aerosol foam formulation of calcipotriol and betamethasone has no impact on HPA axis and calcium homeostasis in patients with extensive psoriasis vulgaris. *J Cutan Med Surg.* 2016;20(1):44–51.
5. Stein Gold L, Lebwohl M, Menter A, et al. Aerosol foam formulation of fixed combination calcipotriene plus betamethasone dipropionate is highly efficacious in patients with psoriasis vulgaris: pooled data from three randomized controlled studies. *J Drugs Dermatol.* 2016;15(8):951–957.
6. Bieber T. Atopic dermatitis. *Ann Dermatol.* 2010;22(2):125–137.
7. Sohn A, Frankel A, Patel RV, Goldenberg G. Eczema. *Mt Sinai J Med.* 2011;78(5):730–739.
8. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol.* 2011;131(1): 67–73.
9. Fujiyama T, Ito T, Umayahara T, et al. Topical application of a vitamin D3 analogue and corticosteroid to psoriasis plaques decreases skin infiltration of T H 17 cells and their ex vivo expansion. *J Allergy Clin Immunol.* 2016;138(2):517–528.e5.
10. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti–interleukin-17–receptor antibody for psoriasis. *N Engl J Med.* 2012;366(13):1181–1189.
11. Aggarwal S, Ghilardi N, Xie MH, et al. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. *J Biol Chem.* 2003;278(3):1910–1914.
12. Kim ES, Frampton JE. Calcipotriol/ betamethasone dipropionate foam: a review in plaque psoriasis. *Drugs.* 2016;76(15):1485–1492.
13. Smith E, Pincus S, Donovan L, Holick M. A novel approach for the evaluation and treatment of psoriasis. Oral or topical use of 1,25-dihydroxyvitamin D3 can be a safe and effective therapy for psoriasis. *J Am Acad Dermatol.* 1988;19(3):516–528.
14. Kobayashi T, Hashimoto K, Yoshikawa K. Growth inhibition of human keratinocytes by a new vitamin D3 analogue in vitro. *J Dermatol Sci.* 1998;16(2):158–164.
15. Kim GK. The rationale behind topical vitamin d analogs in the treatment of psoriasis: where does topical calcitriol fit in? *J Clin Aesthet Dermatol.* 2010;3(8):46–53.
16. Uva L, Miguel D, Pinheiro C, et al. Mechanisms of action of topical corticosteroids in psoriasis. *Int J Endocrinol.* 2012;2012:561018.
17. Fleming C, Ganslandt C, Guenther L, et al. Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study. *Eur J Dermatol.* 2010;20(4):465–471.
18. Papp KA, Guenther L, Boyden B, et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. *J Am Acad Dermatol.* 2003;48(1):48–54.
19. Lind M, Nielsen KT, Schefe LH, et al. Supersaturation of calcipotriene and betamethasone dipropionate in a novel aerosol foam formulation for topical treatment of psoriasis provides enhanced bioavailability of the active ingredients. *Dermatol Ther (Heidelb).* 2016;6(3):413–425.
20. Paul C, Stein Gold L, Cambazard F, et al. Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis

vulgaris: randomized, controlled PSOABLE study. *J Eur Acad Dermatol Venereol.* 2017;31(1):119–126.
21. Asche CV, Kim M, Feldman SR, et al. Budget impact model in moderate-to-severe psoriasis vulgaris assessing effects of calcipotriene and betamethasone dipropionate foam on per-patient standard of care costs. *J Med Econ.* 2017;20(9):1000–1006.
22. Fowler JF Jr, Hebert AA, Sugarman J. DFD-01, a novel medium potency betamethasone dipropionate 0.05% emollient spray, demonstrates similar efficacy to augmented betamethasone dipropionate 0.05% lotion for the treatment of moderate plaque psoriasis. *J Drugs Dermatol.* 2016;15(2):154–162.
23. Stein Gold L, Jackson JM, Knuckles ML, Weiss JS. Improvement in extensive moderate plaque psoriasis with a novel emollient spray formulation of betamethasone dipropionate 0.05. *J Drugs Dermatol.* 2016;15(3):334–342.
24. Rigopoulos D, Palmieri R, Iorizzo M. Phase-2 controlled study to assess the efficacy of two new nail solutions in the treatment of nail psoriasis. *J Am Acad Dermatol.* 2016;74(5):S1:AB137.
25. ClinicalTrials.gov. Study to Evaluate the Efficacy and Safety of P-3073 Nail Solution in the Treatment of Mild to Moderate Psoriatic Fingernail/s. Available at: https://clinicaltrials.gov/ct2/show/NCT03079973. Accessed April 5, 2019.
26. Cantoresi F, Sorgi P, Arcese A, et al. Improvement of psoriatic onychodystrophy by a water-soluble nail lacquer. *J Eur Acad Dermatol Venereol.* 2009;23(7):832–834
27. Cantoresi F, Caserini M, Bidoli A, et al. Randomized controlled trial of a water-soluble nail lacquer based on hydroxypropyl-chitosan (HPCH), in the management of nail psoriasis. *Clin Cosmet Investig Dermatol.* 2014;7:185–190.
28. ClinicalTrials.gov. AN2728 Topical Ointment to Treat Mild-to-Moderate Plaque-Type Psoriasis. Available at: https://clinicaltrials.gov/ct2/show/NCT01300052. Accessed August 3, 2018.
29. Rizvi S, Chaudhari K, Syed BA. The psoriasis drugs market. *Nat Rev Drug Discov.* 2015;14(11):745–746.
30. ClinicalTrials.gov. Efficacy Study Comparing Topical M518101 and Vitamin D3 in Adult Psoriasis Patients. Available at: https://clinicaltrials.gov/ct2/show/NCT01989429. Accessed August 3, 2018.
31. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol.* 2012;83(12):1583–1590.
32. Schafer PH, Parton A, Capone L, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal.* 2014;26(9):2016–2029.
33. Crowley J, Thaçi D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol.* 2017;77(2):310–317.
34. Lee EB, Lebwohl MG, Wu JJ. Treatment of psoriasis with crisaborole. *J Dermatolog Treat.* 2019;30(2):156–157.
35. Alves de Medeiros AK, Speeckaert R, Desmet E, et al. JAK3 as an emerging target for topical treatment of inflammatory skin diseases. *PLoS One.* 2016;11(10):e0164080.
36. Srivastava A, Ståhle M, Pivarcsi A, Sonkoly E. Tofacitinib represses the Janus kinase-signal transducer and activators of transcription signalling pathway in keratinocytes. *Acta Derm Venereol.* 2018;98(8):772–775.
37. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. *Br J Dermatol.* 2015;173(4):949–961.
38. Papp KA, Bissonnette R, Gooderham M, et al. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a Phase 2b randomized clinical trial. *BMC Dermatol.* 2016;16(1):15.
39. Sano S, Chan KS, Carbajal S, et al. Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. *Nat Med.* 2005;11(1):43–49.
40. Lebwohl M, Poulin Y. Tazarotene in combination with topical corticosteroids. *J Am Acad Dermatol.* 1998;39(4 Pt 2):S139–S143.
41. Gollnick H, Menter A. Combination therapy with tazarotene plus a topical corticosteroid for the treatment of plaque psoriasis. *Br J Dermatol.* 1999;140 Suppl 54:18–23.
42. Sugarman JL, Gold LS, Lebwohl MG, et al. A phase 2, multicenter, double-blind, randomized, vehicle controlled clinical study to assess the safety and efficacy of a halobetasol/tazarotene fixed combination in the treatment of plaque psoriasis. *J Drugs Dermatol.* 2017;16(3):197–204.
43. Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: results of 2 Phase 3 randomized controlled trials. *J Am Acad Dermatol.* 2018;79(2):287–293.
44. Bausch Health. FDA Issues Complete Response Letter For DUOBRII™ (Halobetasol Propionate and Tazarotene) Lotion. Available at: https://ir.bauschhealth.com/news-releases/2018/06-18-2018-130118399. Accessed April 1 2019.
45. ClinicalTrials.gov. An Efficacy and Safety Study of PH-10 Aqueous Hydrogel for the Treatment of Plaque Psoriasis. Available at: https://clinicaltrials.gov/ct2/show/NCT00941278. Accessed April 1, 2019.
46. ClinicalTrials.gov. Randomized Study of PH-10 for Psoriasis. Available at: https://clinicaltrials.gov/ct2/show/NCT01247818. Accessed April 1, 2019.
47. ClinicalTrials.gov. A Phase 2 Study of Cellular and Immunologic Changes in the Skin of Subjects Receiving PH-10 Available at: https://clinicaltrials.gov/ct2/show/NCT02322086. Accessed April 1, 2019.
48. Provectus Pharmaceuticals (n.d.). PH-10 for Psoriasis. Available at: http://www.provectusbio.com/ph-10-for-psoriasis. Accessed August 8, 2018.
49. Provectus Inc. (2017). PRovectus Announces Results from Mechanism of Action Study of Topical PH-10 for the Treatment of Psoriasis. Available at: https://globenewswire.com/news-release/2017/11/30/1211817/0/en/PROVECTUS-ANNOUNCES-RESULTS-FROM-MECHANISM-OF-ACTION-STUDY-OF-TOPICAL-PH-10-FOR-THE-TREATMENT-OF-PSORIASIS.html. Accessed August 8, 2018.
50. Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof Is a natural AhR agonist that resolves skin inflammation in mice and humans. *J Invest Dermatol.* 2017;137(10):2110–2119.
51. Bissonnette R, Bolduc C, Maari C, et al. Efficacy and safety of topical WBI-1001 in patients with mild to moderate psoriasis:

results from a randomized double-blind placebo-controlled, phase II trial. *J Eur Acad Dermatol Venereol.* 2012;26(12):1516–1521.
52. Zhao L, Chen X, Cai L, et al. Randomized, double-blind, placebo-controlled, multiple-dose study of the safety, tolerability and pharmacokinetics of benvitimod, a candidate drug for the treatment of psoriasis. *J Clin Pharm Ther.* 2014;39(4):418–423.
53. Mehta AB, Nadkarni NJ, Patil SP, et al. Topical corticosteroids in dermatology. *Indian J Dermatol Venereol Leprol.* 2016;82(4): 371–378.
54. Bäumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets.* 2007;6(1):17–26.
55. Kumar N, Goldminz AM, Kim N, Gottlieb AB. Phosphodiesterase 4-targeted treatments for autoimmune diseases. *BMC Med.* 2013;11:96.
56. Dong C, Virtucio C, Zemska O, et al. Treatment of skin inflammation with benzoxaborole phosphodiesterase inhibitors: selectivity, cellular activity, and effect on cytokines associated with skin inflammation and skin architecture changes. *J Pharmacol Exp Ther.* 2016;358(3):413–422.
57. Freund YR, Akama T, Alley MR, et al. Boron-based phosphodiesterase inhibitors show novel binding of boron to PDE4 bimetal center. *FEBS Lett.* 2012;586(19):3410–3414.
58. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016;75(3):494–503.e6.
59. Cheape AC, Murrell DF. 2% Crisaborole topical ointment for the treatment of mild-to-moderate atopic dermatitis. *Expert Rev Clin Immunol.* 2017;13(5):415–423.
60. Ahmed A, Solman L, Williams HC. Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal. *Br J Dermatol.* 2018;178(3): 659–662.
61. Hanifin JM, Ellis CN, Frieden IJ, et al. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): a phase-II randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol.* 2016;75(2):297–305.
62. Ohba F, Matsuki S, Imayama S, et al. Efficacy of a novel phosphodiesterase inhibitor, E6005, in patients with atopic dermatitis: an investigator-blinded, vehicle-controlled study. *J Dermatolog Treat.* 2016;27(5): 467–472.
63. Furue M, Kitahara Y, Akama H, et al. Safety and efficacy of topical E6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: results of a randomized, vehicle-controlled, multicenter clinical trial. *J Dermatol.* 2014;41(7):577–585.
64. Nemoto O, Hayashi N, Kitahara Y, et al. Effect of topical phosphodiesterase 4 inhibitor E6005 on Japanese children with atopic dermatitis: results from a randomized, vehicle-controlled exploratory trial. *J Dermatol.* 2016;43(8):881–887.
65. Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol.* 2016;175(5):902–911.
66. Cotter DG, Schairer D, Eichenfield L. Emerging therapies for atopic dermatitis: JAK inhibitors. *J Am Acad Dermatol.* 2018;78(3S1):S53–S62.
67. Nakagawa H, Nemoto O, Yamada H, et al. Phase 1 studies to assess the safety, tolerability and pharmacokinetics of JTE-052 (a novel Janus kinase inhibitor) ointment in Japanese healthy volunteers and patients with atopic dermatitis. *J Dermatol.* 2018;45(6):701–709.
68. Kim JE, Kim JS, Cho DH, Park HJ. Molecular mechanisms of cutaneous inflammatory disorder: atopic dermatitis. *Int J Mol Sci.* 2016;17(8). pii: E1234.
69. ClinicalTrials.gov. Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of the Topical Formulation SB011 Applied to Lesional Skin in Patients With Atopic Eczema. Available at: https://clinicaltrials.gov/ct2/show/NCT02079688. Accessed September 9, 2018.
70. Edwards T, Patel NU, Blake A, et al. Insights into future therapeutics for atopic dermatitis. *Expert Opin Pharmacother.* 2018;19(3): 265–278.
71. Bissonnette R, Poulin Y, Zhou Y, et al. Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial. *Br J Dermatol.* 2012;166(4):853–860. JCAD