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Effective Topical Agents and Emerging Perspectives in the Treatment of Psoriasis

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Abstract and Introduction

Abstract

Psoriasis is one of the most common inflammatory skin diseases. The mild form of psoriasis is usually treated with topical medications and phototherapy, whereas conventional systemic therapies, including retinoids, cyclosporine and methotrexate, are used for the treatment of moderate-to-severe psoriasis. The therapeutic approach has been revolutionized over the past decade by the introduction of biologic agents or 'small molecules' that have been proven to have striking clinical efficacy. This review highlights the most effective topical antipsoriatic treatments, focusing on emerging promising topical drugs that are currently being tested in ongoing clinical trials.

Psoriasis as a Complex Immune-mediated Disorder

Psoriasis is a chronic inflammatory skin disease that affects approximately 2–3% of the Caucasian population.[1] Red and scaly plaques, usually localized at the scalp, elbows, knees and buttocks, characterize the most common form of psoriasis, so-called 'plaque-type psoriasis'. Histologically, it is featured by a marked thickening of the epidermis and cutaneous infiltration of inflammatory cells, and by an increase in the number of dilated blood vessels in the upper dermis. The differentiation of keratinocytes is extensively altered in psoriasis: the maturation of keratinocytes from the basal layer to the cornified layer, which in normal skin lasts for approximately 28 days, is shortened to 5 days.[2] This shortened maturation is associated with an evident reduction of the granular layer, with an aberrant terminal differentiation of keratinocytes, which is mainly reflected by parakeratosis.

Initially, it was believed that the pathogenic mechanism exclusively involved keratinocytes.[3] However, several observations supported the view that T cells played a key role in the pathogenesis of psoriasis and, in particular, T_h1 cells, producing IFN-γ, TNF-α and IL-2, were thought to be the specific T-cell subset involved in psoriatic lesion formation. Recently, a new subset of effector $CD4^+$ T cells, known as T_h17 cells, has been discovered to be involved in psoriasis pathogenesis.[4,5] T_h17 cells are developmentally and functionally distinct from T_h1 and T_h2 cells, and they are defined by their ability to synthesize IL-17A, IL-17F and IL-22.[6–8] The differentiation, proliferation and survival of Th17 are dependent on IL-6, TGF, IL-1β, IL-23 and IL-21.[9,10] In particular, IL-23 is crucial for Th17 maintenance and to drive expansion and pathogenicity at later stages of Th17 development.[11] Structurally, IL-23 is similar to IL-12 because they share a common p40 subunit that is covalently linked to either a p35 or p19 subunit to form IL-12 or IL-23, respectively. Activated myeloid dendritic cells secrete IL-23, driving T-cell differentiation toward Th17 subset, and also release IL-12, inducing Th1 differentiation.[12]

Conventional treatments act as nonspecific immunomodulants that broadly suppress the inflammatory response characterizing the psoriatic plaque formation. Their efficacy is variable and associated with organ-specific toxicity. Instead, available biologic agents, as well as new topical drugs, target key cytokines or specific inflammatory pathways determining a highly selective suppression of the immune activation.

Psoriasis severity is the most important parameter that drives the choice of treatment, and it is measured by a well-established index, called the Psoriasis Area and Severity Index (PASI). It is also commonly used in clinical trials to evaluate the therapeutic response to systemic treatments, together with the physician's global assessment (PGA).

However, PASI is seldom used to measure the efficacy of topical products, as it is not very sensitive in patients with

less than 5–10% body surface area (BSA) or in those patients who had a PASI <3.[13]

An effective and standardized approach that measures the therapeutic response of small levels of psoriasis is needed. Some assessment tools have been recently introduced for measuring mild or circumscribed psoriasis, including overall lesion assessment and target lesion severity scores. This latter evaluates scale, infiltration and erythema of a single lesion that is considered a target for assessing the response to treatment. As suggested by Feldman *et al*., it might be effectively used in clinical trials and, if necessary, it might be supported by PGA and quality-of-life measures.[13]

Another tool that could be proven valuable as responder index is the National Psoriasis Foundation Psoriasis Score.[13]

Other factors, including comorbidities, need to be considered for selecting the optimal therapeutic strategy. Indeed, growing evidence has shown an association with an increased risk of cardiovascular mortality, the metabolic syndrome, obesity and Type 2 diabetes compared with the general population, leading to a new concept of psoriasis as systemic disease.[14,15] Moreover, patients with psoriasis have a higher risk of developing depression or anxiety, affecting social, occupational, sexual and financial aspects of their life and even causing them to experience suicidal feelings.[16,17]

Patients are often dissatisfied with current therapeutic approaches, and their compliance to treatment is poor. Therefore, the management of psoriasis is challenging.

Conventional Topical Agents

The majority of patients (70–80%) are affected by mild-to-moderate psoriasis, having a limited involvement of the skin that could be treated with topical medications or phototherapy.[18] In particular, in childhood, most children show a mild form of psoriasis that might be generally well controlled with topical compounds.

Although most psoriatic patients require a topical therapy, during the last few decades, the authors have observed the introduction of several new agents or new formulations in this class of drugs into daily clinical practice. In fact, several promising chemical entities that had been designed failed proof-of-concept studies.

Classically, corticosteroids, vitamin D_3 analogs and retinoids represent the first-line treatment of mild psoriasis. In addition, new emerging drugs that have been developed over the past few years will potentially enlarge the therapeutic armamentarium.

Corticosteroids

Corticosteroids still represent the milestone in the topical treatment of psoriasis in all age groups.[19] Owing to their anti-inflammatory and antiproliferative properties, they reduce erythema, scaling and pruritus in psoriasis. In particular, they show immunomodulating effects at different stages: inhibition of monocyte and neutrophil recruitment, reduction of the expression of inflammatory and proliferative mediators and suppression of *de novo* synthesis of lipocortin, which, in turn, regulates the arachidonic acid cascade.

Corticosteroids, ranging from low to high potency, are available in a variety of formulations including creams, emollient cream, ointment, gel, spray, lotion, solution, nail lacquer, tape and foam. Cortisol, the basic steroidal molecule, is composed of 17 carbon atoms (C-atoms) in a four-ring complex.[20–22] Modifying or substituting the ring structures or the side chains of cortisol molecule, a broad range of topical corticosteroids may be obtained and, according to their therapeutic potential, they may be classified into four classes: mild, medium, potent and very potent.

The disease severity, the site of application and patient's preferences determine the choice of appropriate formulation.[18,23] Furthermore, steroids are absorbed at different rates from different parts of the body. The same

steroid may have a rapid absorption in a particular part of the body, while in other parts, it may result ineffective.

Usually, lower potency corticosteroids are used in childhood and on sensitive skin sites including the face, axillae, diaper area and gluteal cleft, whereas hyperkeratotic areas, such as the palms and soles, or chronic lesions require high-potency corticosteroids. High-potency agents can be used for a limited period of 2–4 weeks, no more than twice daily and at a dose of no more than 50 g/week, although they are often used in the longer term in clinical practice.[18] Indeed, several long-term strategies based on potent corticosteroids could be considered, including intermittent therapy, weekend therapy, combined therapeutic schemes with other topical medications or milder corticosteroids. Importantly, in order to improve safety for long-term steroid treatment and to detect side effects at the earliest stage, careful medical supervision should be performed.[18,24]

The efficacy rates of ultrapotent corticosteroids range from moderate or better improvement of PGA in 58% of patients, to overall improvement of PGA in 92% of patients, while with mild corticosteroids, PGA improvement has been reported as excellent or good in 41% of patients and as good or better in 83% of treated patients.[25–28]

Local side effects including skin atrophy, striae, telangiectasia, purpura, rosacea, acneiform dermatoses and rebound erythema may occur because of long-term therapies at the site of application, particularly at steroid-sensitive areas. Another relevant side effect of chronic application of corticosteroids is tachyphylaxis.[29,30] The evaluation of frequency and relevancy of side effects is challenging, since most clinical trials only assessed the safety and efficacy of topical corticosteroids for a few weeks.

In a long-term, three-arm study assessing safety and efficacy of 52 weeks of combined therapy with calcipotriol/betamethasone dipropionate (group I), 52 weeks of alternating 4-week periods of the two-compound product and calcipotriol (group II), or 4 weeks of the two-compound product followed by 48 weeks of calcipotriol (group III), adverse drug reactions associated with long-term topical corticosteroid therapy were observed in 4.8, 2.8 and 2.9% of patients in groups I, II and III, respectively, although the difference was not statistically significant. The most common side effects reported were skin atrophy and folliculitis.[31]

Often, side effects may occur in steroid-sensitive sites or they may be related to steroid nonlabel application or to overuse for a long period of time, particularly if patients use steroids chronically without any control or monitoring by physicians.[18]

Rarely, a prolonged and widespread use of potent corticosteroids could cause suppression of the hypothalamic–pituitary–adrenal axis in children because of increased skin surface to body mass ratio.[18]

Application should be gradually tapered down in order to avoid rebound effects. To minimize the side effects, it could be useful to consider a switch to lower potency corticosteroids after successful treatment with potent agents. Moreover, 'weekend therapy' or 'pulse therapy' should be considered for reducing the amount of corticosteroids, as well as combination therapy or rotation therapy using alternative nonsteroidal drugs such as coal tar, anthralin, calcipotriene and topical calcineurin inhibitors.[32]

Vitamin D_3 Derivatives

Vitamin D_3 analogs were introduced in the early 1990s since oral vitamin D was demonstrated to be effective in improving psoriasis. Three vitamin D3 analogs are commonly used for the treatment of psoriasis: calcitriol, calcipotriol and tacalcitol.

They bind to the vitamin D receptor, normalizing keratinocyte proliferation and differentiation and modulating the immune response. Indeed, lesional psoriatic skin is characterized by high levels of keratinocyte proliferation markers and by altered expression of epidermal keratinocyte differentiation markers (e.g., involucrin and filaggrin) that showed a normalization of the expression levels, similar to normal skin, along with topical vitamin D_3 analogs.[33,34]

Furthermore, this class of topical agents may also interfere with the immune system, inhibiting the activation of T cells and dendritic cells, and stimulating regulatory T helper cells.[35,36] Calcipotriol is available in the form of a cream, solution or ointment for the treatment of plaque-type psoriasis, scalp psoriasis and nail psoriasis, respectively. It has been found to be effective and safe, even when it is associated with sun exposure. A randomized, double-blind, within-patient trial of 50 patients treated with 25, 50 and 100 µg/g calcipotriol ointment demonstrated a marked effectiveness of calcipotriol with an improvement of 40, 63 and 80% at the three doses, respectively.[37]

Tacalcitol is a synthetic vitamin D_3 analog, which is administered once daily. Several studies have assessed the efficacy and safety of tacalcitol and have reported successful clinical outcomes.[38–40]

Treatment with calcitriol shows better tolerability in sensitive and irritated areas of the skin, and thus it may be used in psoriatic children. In a study of 258 patients, calcitriol showed a similar efficacy to betamethasone dipropionate after 6 weeks of treatment and a more prolonged remission at 8 weeks.[41] Another large study of 253 patients demonstrated long-term efficacy associated with a satisfactory safety profile.

Other vitamin D_3 derivatives have been investigated for topical use, such as maxacalcitol and becocalcidiol. A study reported a superior efficacy of maxacalcitol versus calcipotriol, although a burning sensation in treated lesions was a common adverse event.[42]

Local side effects are usually not severe, and they may include erythema, burning, pruritus and edema. Nevertheless, although limited information is available, minimal systemic effects on calcium levels and calcium secretion seem to characterize the maxacalcitol safety profile.

Combined Therapy With Vitamin D3 Derivatives & Corticosteroids

Two-compound products consisting of calcipotriol and betamethasone dipropionate have recently been introduced. This formulation, combining the action of calcipotriol (regulation of keratinocyte differentiation and antiproliferative effects) with the anti-inflammatory effects of steroids, enhances the effectiveness of this compound and, presumably, it could offer the possibility of reduction in the dose of either or both single agents, with a potential decrease in the occurrence of their side effects, as assumed by some authors.[43–46] However, patients treated with the two-compound formulation showed a reduction of the local side effects induced by calcipotriol (irritant contact dermatitis and erythema), although steroid-related side effects were still observed.[31,44]

Ortonne *et al.* demonstrated that daily application of the two-compound formulation for 4 weeks, followed by calcipotriol as a monotherapy, is more effective than tacalcitol therapy for 8 weeks.[47]

A multicenter study including 285 patients demonstrated the efficacy and safety of this combined formula applied once daily and followed by 8-week therapy with calcipotriol.[48] Another three large Phase III, multicenter, prospective, randomized, blinded clinical studies confirmed superior efficacy of the two-compound product compared with tacalcitol or either agent alone.[49–51]

The long-term efficacy and safety of this formulation has been reported in a 52-week study of 828 patients that showed an improvement in PGA ranging from 69 to 74% of patients continuously treated with the combination compound of calcipotriol and betamethasone dipropionate, achieving clear or almost clear status with no serious adverse events.[31]

A Phase II clinical trial compared calcipotriol plus betamethasone dipropionate ointment with a new cutaneous spray ointment compound, LEO 90100 (LEO Pharma), which is now being evaluated in three Phase II studies.[101]

An increasing number of medications, particularly for the scalp, have been developed into innovative, easy-to-use formulations.

Potentially, ointments might have a negative impact on adherence, and therefore a lipophilic, nonalcoholic gel vehicle was developed. The two-compound gel formulation, as well as the two-compound ointment, has the same active ingredients (calcipotriol and betamethasone dipropionate) and the same therapeutic scheme (once daily).[52]

A Phase II and a Phase III study investigating the two-compound gel in patients with psoriasis have recently been completed, and the gel formulation has already been approved in several countries for the treatment of scalp psoriasis.

The Phase II trial was a multicenter, prospective, randomized, double-blind study including 364 patients with psoriasis vulgaris. After 8 weeks of treatment, the two-compound formulation showed a better efficacy profile in both PASI and PGA scores compared with calcipotriol gel and gel vehicle, while the combined compound gel was superior to betamethasone dipropionate gel in PGA score at week 8.[53]

In an 8-week, Phase III trial of 458 patients, 39.9% of the two-compound gel group was assessed as 'clear or almost clear', compared with 17.9% in the tacalcitol arm ($p < 0.001$) and 5.5% in the gel vehicle arm ($p < 0.001$).[54]

The gel formulation proved to be safe and well tolerated in both Phase II and Phase III clinical trials; only mild or moderate adverse events such as pruritus and skin irritation were reported.

Retinoids

Tazarotene represents the only topical retinoid that can be used for plaque psoriasis as gel or cream in 0.05 and 0.1% formulations. In keratinocytes, tazarotene regulates transcription signaling through the retinoic acid receptors (RAR)-γ, RAR-β and RAR-α, thus inhibiting proliferation and normalizing differentiation. It also acts as inflammation-suppressing agent.[55]

The efficacy of once-daily application of both cream and gel tazarotene has been demonstrated after 12 weeks of treatment, with a statistically significant improvement of skin lesions in four different trials. Two placebo-controlled trials of 1303 patients showed satisfactory efficacy of 12-week treatment with 0.1 and 0.05% tazarotene cream in improving plaque thickness, erythema and scale.[56]

The use of tazarotene is limited by quite common side effects such as erythema, irritation and burning that may occur with protracted use, and they might be minimized by using the cream instead of the gel formulation, lowering the concentration, and performing a short-contact therapy or alternate-day applications.[57]

Tazarotene can be used in combination with corticosteroids, lessening tazaroten's side effects, or UVB, although the combination with ultraviolet radiation induces both photosensitivity and increased efficacy. It is contraindicated in pregnancy and in nursing women because of its teratogenic potential.[58]

Tars & Anthralin

Coal tar has been used for more than 100 years for the treatment of psoriasis. Coal tar and wood tars (birch, pine and beech) are available as topical antipsoriatic agents in different formulations, including ointment, cream, gel, lotion, shampoo and soap. The mechanism of action of coal tar is not well understood, but it seems to suppress DNA synthesis and, thus, to reduce keratinocyte proliferation. Tar-based formulations are indicated for the treatment of chronic stable forms of plaque-type psoriasis, scalp psoriasis and palmoplantar psoriasis, whereas their use might be limited in sensitive areas, including the genital area and flexural areas, because of their irritant potential. Although it is a well-established antipsoriatic treatment, few controlled studies have been reported in the literature. Coal tar may be used as a monotherapy or in association with UVB (Goëckerman regimen). Its use is limited because of poor patient acceptance due to cosmetic inelegance, including staining of clothes and a potent tar odor that is present in almost all products. Additional potential adverse effects include irritant contact dermatitis, folliculitis and photosensitivity to UVA light. There is not any particular caution to its use during pregnancy, whereas its use is not recommended in

association with UVA because of an increased risk of skin cancer.[59]

Anthralin shows both antiproliferative activity on keratinocytes and a marked anti-inflammatory effect. As observed for coal tar, anthralin reduces cell proliferation blocking DNA synthesis and restoring physiological keratinization. It seems that all the effects exerted by anthralin are due to oxidative metabolic processes, with the subsequent release of reactive oxygen species.[60,61] Anthralin exerts anti-inflammatory effects, suppressing the release of IL-6, IL-8 and TNF-α from monocytes.[62] The anti-inflammatory mechanism is not well understood since oxygen free radicals constitute important mediators of the inflammatory response.

Keratolytics

Keratolytics represent a class of therapeutic compounds characterized by the capability of decreasing cell-to-cell cohesion in the stratum corneum and, therefore, promoting the physiologic shedding process. Salicylic acid is a keratolytic agent that is used to reduce hyperkeratosis and increase the absorption of other medications. It is the oldest keratolytic agent used in dermatology at low concentrations, usually ranging from 2 to 6%. Higher concentrations could be used with caution for massive and cohesive hyperkeratosis, as may occur in palmoplantar areas. The mechanism of action is not well understood, but it probably includes reduction of keratinocyte-to-keratinocyte adhesion and, pH of the stratum corneum.[63] In the literature, no placebo-controlled studies have been reported, and it is usually reported as coadjuvant for combined therapeutic schemes with corticosteroids or calcineurin inhibitors.

Extensive use may be correlated with important side effects such as salycilate toxicity (salicylism) characterized by dizziness, headache, confusion, and ringing or buzzing in the ears.[64] Hence, systemic absorption may occur and, thus, it should not be used in combination with oral salicylate drugs or it cannot be applied to more than 20% of the BSA. Moreover, it should be used with caution in patients with abnormal hepatic or renal function.

Other keratolytic agents include α-hydroxy acids (mainly lactic acid and propylene glycol), urea and glycerin.

Topical Calcineurin Inhibitors

Topical calcinuerin inhibitors could be taken into consideration as a maintenance therapy after a satisfactory steroid therapy, possibly by reducing corticosteroids gradually and introducing calcineurin inhibitors as substitute therapeutic agents. They could constitute a valid alternative to corticosteroids because of their ability to suppress T-cell activation and proliferation. Indeed, by blocking calcineurin phosphatase, they prevent the dephosphorylation of the nuclear factor of activated T cells, which leads to inhibition of the activation of T cells and the production of proinflammatory cytokines including TNF-α, IFN-γ and IL-2, which is a key cytokine in the activation and amplification of T-cell response.[65]

Pimecrolimus (1.0%) and tacrolimus (0.03 and 0.1%) have been proven to be effective, well tolerated and safe in the treatment of atopic dermatitis, whereas their use in psoriasis is off-label, and their efficacy is still controversial.[66,67] Their efficacy seems to be limited because of their poor penetration into hyperkeratotic psoriatic plaques, and thus they might be considered as optimal therapeutic option in treating intertriginous areas and more sensitive body sites such as the face where the absorption is naturally increased.[68,69] However, in order to increase the limited penetration of these agents, they could be applied under occlusion or in combination with keratolytics such as salicylic acid and urea.

Recent clinical trials and case series showed an impressive efficacy in treating facial and flexural psoriasis. In an open-label clinical trial of 21 patients, tacrolimus induced complete clearance after 57 days of treatment in 81% of patients.[70]

A randomized, double-blinded, controlled, multicenter study enrolling 167 patients demonstrated clearance or excellent improvement in 65.2% of the tacrolimus ointment group compared with control group after an 8-week

treatment period.[71]

In a study of 21 patients treated with 0.1% tacrolimus ointment, applied twice daily for 4 weeks without occlusion, 10 (47.6%) and 9 (42.9%) patients experienced a complete or good response, respectively.[72]

For the treatment of genital psoriasis, an open-label study was performed using topical tacrolimus 0.1% ointment, applied twice daily for 8 weeks with a follow-up period of 4 weeks.[68]

The other calcineurin inhibitor, pimecrolimus, has been shown to be effective and well tolerated for intertriginous and facial psoriasis. In a double-blind, randomized, vehicle-controlled study of 57 patients, 8 weeks of pimecrolimus treatment induced an improvement in 82% of patients compared with 41% of the vehicle group.

On the basis of Investigator Global Assessment, good efficacy of 1% pimecrolimus cream has also been observed in a double-blind, randomized, controlled trial involving 57 patients with moderate-to-severe inverse psoriasis. More than half of patients (54%) were clear or almost clear after 2 weeks of treatment compared with 21% of the vehicle arm, and by week 8, the percentage increased to up to 71%.[72]

Lebwohl *et al*. confirmed tacrolimus as being effective for the treatment of facial and flexural psoriasis, showing marked improvement in 66.7% of patients compared with 36.8% of the vehicle arm.[70]

Regarding the safety profile, calcineurin inhibitors appear to be safe, since only mild side effects including itching, stinging and the feeling of warmth may occur, and they do not show the typical long-term side effects of steroids, although no extensive studies so far have confirmed their safety in psoriasis treatment.

New Perspectives for Topical Therapy

Blockade of Neurogenic Inflammation

A role for the nervous system in the biology of psoriasis has been hypothesized since psycological conditions (i.e., emotional stress, anxiety and depression) have also been identified as triggering and exacerbating factors.[73,74]

Marked proliferation of cutaneous nerves and increased levels of neuropeptides have been detected in lesional psoriatic skin, potentially contributing to the development of psoriasis.[74]

The peripheral nervous system may mechanistically contribute to the cutaneous inflammatory response releasing neuropeptides such as substance P, vasoactive intestinal peptide and nerve growth factor (NGF) that are able to modulate the immune system.[75] In particular, NGF seems to play a role in keratinocyte proliferation, angiogenesis, T-cell activation, expression of adhesion molecules and proliferation of cutaneous nerves, thus contributing to psoriatic plaque formation.[76]

Targeting the nervous system could represent a new and efficacious therapeutic approach, as suggested by the efficacy of neuropeptide-modulating agents such as capsaicin, somatostatin and peptide T in improving psoriasis.[77]

Clinical and histological improvement of psoriasis was observed in a xenotransplant model treated with K252a, a high-affinity NGF receptor blocker.[78]

On the basis of these promising data, a topical agent, namely, CT327 (Creabilis SA), has been developed. It is a TrkA kinase inhibitor (a pegylated derivative of K-252a), which has successfully completed Phase I and Phase II studies, and is currently under evaluation in a further Phase II study, assessing the effectiveness, safety and tolerability of three dose strengths of CT327 ointment (0.05, 0.1 and 0.05%) compared with placebo, applied twice daily for up to 8 weeks.[101]

Janus-associated Kinase Inhibitors

Janus-associated kinases (JAKs) are a family of protein tyrosine kinases including JAK1, JAK2, JAK3 and TYK2. Activating signal trasducers and activators of transcription (STAT), JAKs broadly regulate the expression of key genes mediating keratinocyte proliferation, inflammation, cell activation and survival.[79]

Inflammatory and proliferative mediators implicated in the pathogenesis of psoriasis, including IL-12, IL-23, IL-17, IL-21, IL-22, IL-20 and interferons, signal through the JAK/STAT pathway.[80]

The cornerstone of these highly selective inhibitors is tofacitinib (CP-690,550, Pfizer) which suppresses JAK1 and JAK3 and, to a lesser extent, JAK2 and TYK2 signaling. It was developed as an immunosuppressive agent for the prevention of transplant rejection and for the treatment of immune-mediated diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis.[81]

Systemic treatment with oral tofacitinib resulted in a favorable safety profile with satisfactory efficacy in Phase II clinical trials. Two randomized, double-blind, placebo-controlled Phase III studies are ongoing for psoriasis, and other studies are being performed for different indications.

Recently, a topical formulation of tofacitinib was evaluated in a Phase IIa randomized, double-blind, vehicle-controlled study, but clinical outcomes are not yet available.[101]

A JAK3 inhibitor, ASP-015K (Astellas Pharma), is currently under evaluation in Phase III studies. In addition, INCB018424 (Incyte Corporation) is small molecule with pan-JAK inhibitory activity suppressing the production of inflammatory cytokines related to JAK signaling, such as IL-12, IL-23 and IL-17. Indeed, significant common cytokines signal through JAK/STAT pathway, particularly IL-12 and IL-23 (regulating T-cell differentiation), IL-20 and IL-22 (inducing epidermal hyperplasia), IL-17 and IFN-γ (promoting inflammation).[82,83] Therefore, selective JAK inhibition restrains both keratinocytes proliferation and inflammatory processes, resulting in the improvement of lesional skin thickness, erythema and scaling.[83]

In the first in-human study, Punwani *et al.* assessed the safety, tolerability, pharmacokinetics and efficacy of INCB018424 phosphate cream in three concentrations (0.5, 1.0 and 1.5%). The cream was applied once or twice daily, and it was compared with vehicle and calcipotriene 0.005% cream or betamethasone dipropionate 0.05% cream.[83]

Topical INCB018424 applications were demonstrated to be effective, with a clinical improvement of the lesion score (lesion thickness, erythema and scaling) greater than 50%. No serious adverse events, as well as pharmacologically negligible plasma concentrations, were reported.[83]

MEK1/MEKK1 Inhibitor

E6201 [(3S,4R,5Z,8S,9S,11E)-14-(ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9,10-tetrahydro-1H-2-benzoxacyclotetradecine-1,7(8H)-dione] (Eisai Inc.) is a MEK1/MEKK1 inhibitor exerting a potent anti-inflammatory action suppressing the production of proinflammatory cytokines from leukocytes and keratinocytes.[84] E6201 suppresses *in vitro* lymphocyte activation and proliferation.[85] An important *in vitro* effect is the inhibition of neutrophil migration, reflecting the suppression of IL-8 production from activated human keratinocytes. Muramoto *et al.* observed that topical treatment with E6201 significantly inhibited epidermal hyperplasia in IL-23-treated mice.[84] Moreover, E6201 shows direct antiproliferative activity on cultured keratinocytes; therefore, it may be effective in psoriasis because of distinct effects on both immune cells and keratinocytes.

Using several experimental models of dermatitis, preclinical studies showed that topical administration of E6201 formulated as an ointment or cream was effective in reducing acute edema formation and neutrophil infiltration into mouse skin.[84]

A double-blind, multicenter, Phase II study assessed the efficacy and safety of E6201 topical administration to

preidentified marker lesions in patients with chronic plaque-type psoriasis. The duration of treatment was 8 weeks, followed by a 4-week period without treatment.

Another Phase II trial is currently ongoing to determine the efficacy and safety of six concentrations of topical E6201 gel.[101]

Other Nonsteroidal Anti-inflammatory Agents

WBI-1001 [(2-isopropyl-5-[(E)-2-phenylethenyl] benzene-1,3-diol)] (Welichem Biotech, Inc.) is a new anti-inflammatory, nonsteroidal, small molecule deriving from metabolites of bacterial symbionts of soil living nematodes. Its inflammatory action is due to significant inhibition of the expression of proinflammatory cytokines such as *TNF-α* and *IFN-γ*. This topical synthetic compound has been developed for the treatment of chronic inflammatory skin diseases including psoriasis and atopic dermatitis. Both Phase I and II clinical trials for atopic dermatitis and psoriasis have been performed and completed.[85,86] A randomized, placebo-controlled Phase IIa study including 37 atopic dermatitis patients evaluated the safety, tolerability and efficacy of treatment with WBI-1001 cream at different concentrations, 0.5 and 1.0%, twice daily.[86]

The efficacy of WBI-1001 cream was assessed in a randomized double-blind placebo-controlled, Phase II trial, in which a 62.8% improvement in PGA score was observed when compared with 13.0% for psoriatic patients randomized to placebo. After 12 weeks of treatment, the mean improvement in BSA was 79.1% when compared with an increase of 9.4% ($p < 0.0001$) in the placebo arm. Overall, WBI-1001 has been proven to be safe and well tolerated by psoriasis patients, with very promising effectiveness in controlling disease.[87]

LAS41002 and LAS41004 (Almirall, S.A.) constitute novel interesting nonsteroidal anti-inflammatory agents for the treatment of eczema, and more specifically of psoriasis. LAS41002 is in Phase II trials, while LAS41004 in Phase III trials.[101] These compounds act on a corticosteroid receptor, thus determining both the suppression of inflammation and the inhibition of cellular proliferation. Owing to their different formulations, they could be used for various inflammatory skin conditions.

PH-10 (Provectus Pharmaceuticals) is an aqueous hydrogel formulation of 0.001% rose bengal disodium developed for the treatment of cutaneous skin disorders, specifically psoriasis and atopic dermatitis. In ophthalmology, rose bengal is used as a stain to assess reflex tear production, and it is also in use as an intravenous diagnostic to detect ailments of the liver. A 10% rose bengal disodium formulation is currently under investigation for the treatment of hepatocellular carcinoma, the most common form of liver cancer, because of its selective toxicity to cancer cells via chemoablation.

A total of 217 subjects affected by psoriasis have been treated with PH-10 in Phase I or II clinical trials. A multicenter Phase II study tested different concentration of topical PH-10 (0.002, 0.005 and 0.01%) applied once daily to areas of mild-to-moderate plaque psoriasis. Interestingly, a Phase II study investigated the safety and efficacy of 0.001% PH-10 aqueous hydrogel combined with ambient light exposure or 544 nm light-emitting diodes light illumination at 10 J/cm^2.[101]

Phosphodiesterase Inhibitors

AN2728 [(5-(4-cyanophenoxy)-2,3-dihydro-1-hydroxy-2,1-benzoxaborole)] (Anacor Pharmaceuticals, Inc.) is a synthetic phenoxy benzoxaborole showing inhibitory activity against phosphodiesterase 4 (PDE4) and release of TNF-α, IL-12, IL-23 and other cytokines.[88,89]

AN2728 appeared to be safe and effective in treating psoriatic lesions in three Phase I and five Phase II clinical trials.[102]

Another PDE4 inhibitor, MK-0873 (Merck), was tested in two Phase I trials. In a three-part study, safety and

tolerability were evaluated using 0.5 and 2% MK-0873 cream once or twice daily.[101]

M518101 (Maruho Co., Ltd.) is reported as cytokine blocker–phosphodiesterase inhibitor, and two Phase II clinical trials have been performed to test its safety and efficacy, but no data are available so far.

STAT Inhibitors

STAT proteins are signal trasnducers involved in various cellular processes including growth, survival, inflammation and differentiation. In particular, STAT1/2 regulate the response of immune cells, transducing type I interferon stimuli.

STAT3 is a transcriptional factor that is highly expressed in keratinocytes during the development of psoriatic lesions. It mediates keratinocyte proliferation, differentiation and migration induced by several cytokines representing crucial mediators in psoriasis.[90]

In particular, IL-20 subfamily cytokines, namely IL-22, IL-19, IL-20, IL-24 and IL-26, are able to phosphorylate Stat3 in keratinocytes, and they have been found to be upregulated in lesional psoriatic skin.[91] Furthermore, EGF family growth factors, which are secreted by keratinocytes, activate STAT3, resulting in an autocrine proliferative stimulation.[92]

STA-21 (Kochi University) is a small Stat3 inhibitor suppressing keratinocyte proliferation in a dose-dependent manner through downregulation of c-Myc and cyclin D1.

A nonrandomized trial with a limited number of patients showed a favorable response to STA-21 compared with the vehicle control.[93] As suggested by the authors, further randomized clinical trials are necessary for dose optimization, and it would be interesting to compare this inhibitor with conventional topical agents such as vitamin D_3 derivatives or steroids.

Pan-selectin Antagonists

Selectins play a crucial role in inflammation and immune response since they mediate the adhesion of leukocytes to activated endothelial cells, and thus they regulate rolling and trafficking of blood leukocytes.

Bimosiamose/TBC1269 (Revotar Biopharmaceuticals AG) is a pan-selectin antagonist in development for topical use in psoriasis. It constitutes a small-molecule, anti-inflammatory agent targeting P-selectin, E-selectin and L-selectin that possesses the capability to block leukocyte extravasation.

Bimosiamose/TBC1269 has been demonstrated to be effective in both preclinical and clinical studies. In an open-label observational clinical pilot trial, five patients were treated with daily intralesional injections of Bimosiamose/TBC1269 600 mg for 2 weeks, and reductions in epidermal thickness and lymphocyte infiltration were observed.

A multicenter, randomized, double-blind, placebo-controlled Phase II study has been completed to evaluate the safety and efficacy of Bimosiamose/TBC1269 5% cream in 107 patients with chronic plaque-type psoriasis.[94,95]

Another pan-selectin inhibitor, efomycin M, has been investigated in a mouse model, but clinical trials are still lacking.

Expert Commentary

The great majority of patients (70–80%) are affected by mild or mild-to-moderate psoriasis that it is usually treated with topical medications. Although the skin involvement is limited, psoriasis might have a relevant psychological impact if it affects the genital areas, scalp and face. Conventionally, corticosteroids and vitamin D3 analogs as a combination treatment or monotherapy represent the most common therapeutic agents for first-line treatment.

These therapies may be associated or alternated with other topical therapies such as salicylic acid and coal tar.

The two-compound formulation of calcipotriol/betamethasone dipropionate ointment was found to be effective and well tolerated, although its ointment formulation may reduce adherence to the treatment. Therefore, a new gel formulation has been developed in order to increase the cosmetic acceptability and, consequently, the patients' compliance.

As a matter of fact, greasy, sticky, oily treatment vehicles are not agreeable for many patients, whereas gel and cream formulations show a better ease-of-use and cosmetic acceptability. Indeed, for a satisfactory therapeutic approach, several aspects need to be considered as relevant issues that can cause a poor compliance to the treatment: intolerance to medications, lack of response, cosmetic acceptability, ease-of-use and patient's education.

The therapeutic scheme should suit patients' needs and expectations, and it may represent a tough challenge.

For short-term therapy, corticosteroids represent the most common therapeutic option, whereas for long-term therapy, in order to pursue an optimal corticosteroid-sparing regimen, other compounds should also be taken into consideration. Potent corticosteroids might be replaced or spared using vitamin D_3 analogs, topical retinoids or combined compounds (calcipotriol–betamethasone propionate compound, agents containing both salicylic acid and topical corticosteroids, or tar and topical corticosteroids). This therapeutic scheme would provide satisfactory efficacy with reduced exposure to steroidal agents. An alternative approach may be constituted by calcineurin inhibitors, although their efficacy has only been proven for facial and flexural psoriasis. These sensitive sites cannot be treated with corticosteroids, tazarotene and vitamin D_3 derivatives because of their side effects.

Although topical therapies are suggested for mild-to-moderate psoriasis, they also find application in the treatment of moderate-to-severe forms because they may be useful to reduce the total amount of UV or the systemic agent dosage.

Five-year View

During the last two decades, scientific interest has focused on systemic therapies, particularly on biologics and the so-called 'small molecules'. They selectively target cytokines or enzymes involved in the inflammatory pathways that contribute to the pathogenesis of psoriasis.

The concept of this therapeutic approach has been revolutionary because, rather than determining a broad and nonspecific immunosuppression, they modulate the immune response by blocking key inflammatory mediators that are highly expressed in psoriasis.

Indeed, recent insights into the understanding of the pathogenesis have led to the identification of novel targets for therapy such as mitogen-activated protein kinases, PDE4, the JAK/STAT pathway, NGF receptor and TrkA kinase. This new therapeutic model has been transferred to topical therapy, leading, in the last few years, to a rising number of novel topical agents that have been developed and are currently being tested in Phase I and II clinical trials.

Importantly, in order to increase adherence to treatment and to improve tolerability and cosmetic agreeability, innovative compounds and a wide repertoire of advanced formulations are under investigation.

In the near future, these promising perspectives on new agents and formulations will increase the armamentarium of topical antipsoriatic treatments, improving the management of psoriasis.

Sidebar

Key Issues

- Corticosteroids still represent the cornerstone of topical therapies for psoriasis, together with vitamin

D_3derivatives, although promising alternative therapies will allow avoidance of prolonged use of corticosteroids, limiting their application as a short-term therapy and thus avoiding atrophy, tachyphylaxis, rebound and long-term effects.

- Calcineurin inhibitors constitute a valid alternative to corticosteroids because of their ability to suppress T-cell activation and proliferation. Their efficacy seems to be limited because of their poor penetration into hyperkeratotic psoriatic plaques, and thus they might be considered as the optimal therapeutic option when treating intertriginous areas and more sensitive body sites, such as the face.
- The development of hyperselective therapeutic agents acting at different stages of the psoriasis inflammatory response is ongoing.
- Stat3 inhibitors, JAK1/2 inhibitors, JAK3 inhibitors, MEK1/MEKK1 inhibitors, pan-selectin antagonists and phosphodiesterase 4 inhibitors will potentially represent the new class of topical highly selective drugs.
- A wider therapeutic armamentarium for treating psoriasis will be available in the near future.

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Papers of special note have been highlighted as:
• of interest
•• of considerable interest

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