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Long-term topical management of psoriasis: the road ahead

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ABSTRACT

Topical therapies have been available for the treatment of psoriasis for several decades. Despite this and the availability of several types of topicals, with varying potency, and numerous vehicles of administration, the majority of clinical data and guidance is on short-term use in the management of psoriasis. The aim of this manuscript is to review the unmet needs that exist in the long-term management of psoriasis and provide the dermatology community with an understanding that a treatment regimen with topical therapies could be the best treatment option at least for some phases of this chronic relapsing disease. We present a 'call to action' on the need for clinical alignment on terminology in the field and recommend the term 'long-term management' be adopted as the most appropriate in the context of this manuscript. This expert opinion report provides a detailed review of the limited evidence available regarding long-term use of topical therapies for the management of psoriasis, alongside our key considerations and recommendations to assist dermatologists with the implementation of topicals as part of long-term management strategies. Long-term management should be considered mandatory to ensure patients receive appropriate proactive treatment which may help optimize adherence and long-term outcomes.

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Introduction

Psoriasis is a chronic inflammatory, immune-mediated systemic disease with skin manifestations that typically follow a relapsing and remitting course. The most common form, plaque psoriasis, occurs in ~80–90% of psoriatic patients (1), and is characterized by well-delineated, scaly, itchy, erythematous plaques that commonly affect areas such as the elbows, knees, scalp and sacral region (2,3). The chronic nature of the disease and the substantial impact it has on patient quality of life necessitates long-term management strategies to achieve skin clearance and optimize long-term outcomes (4). Such strategies require regular review and adaptation according to the course of disease and response to treatment.

Approximately 80% of patients with psoriasis have localized, usually mild-to-moderate, disease, which can be treated with topical treatments (5,6) and current guidelines recommend topical therapies as first-line treatment (7,8). Currently approved topical treatments include corticosteroids (used alone or in combination regimens), vitamin D analogs, combined corticosteroid/vitamin D (calcipotriol) formulations, vitamin A derivatives (tazarotene), anthralin, and newer formulations of tar (5). Furthermore, topical preparations containing salicylic acid (3–10%) and urea (3–10%) are frequently used as adjunctive treatment (4). The type of vehicle is an important consideration which can significantly impact efficacy and potency. Traditional

vehicles include lotions, creams, ointments, gels, sprays, powders and, more recently, foams (5). Topical therapies can be used alone or as adjunctive agents with systemic treatment in order to enhance therapeutic outcomes (9). When used with systemic treatment, Bagel et al. noted that 'the topical agent added should be cosmetically acceptable, be dosed preferably once-daily to enhance adherence, and have demonstrated a good efficacy and safety profile' (10).

Although numerous topical treatments are available, there is a paucity of guidance or clinical data regarding their use for the long-term management of psoriasis (4,7,8,11). Indeed, although the National Institute of Health and Care Excellence (NICE) guidelines acknowledge that 'further research on the use of topical agents for maintaining disease control in the long term continues to deserve focused attention' (8), international guidelines generally do not provide complete recommendations regarding long-term maintenance (12–14), e.g. how or when to stop topical therapy. Factors such as medication dosage/schedule, choice of vehicle, patient adherence to medication, and patient concerns about treatment-related toxicities are all key considerations for optimizing clinical outcomes in daily practice (5).

Our aim in this manuscript is to establish an understanding within the clinical community that a treatment regimen with topical therapies should reflect the relapsing/remitting nature of psoriasis, with the expectation that long-term management is

Table 1. Key considerations for long-term use of topical therapies for mild-to-moderate psoriasis.

Treatment goals in the context of long-term management
<ul style="list-style-type: none"> • Efficacy (i.e. skin clearance and clinical tools to assess response) • Patient quality of life • Minimal safety risks • Patient perspective (i.e. what is important to the individual) • Severity of disease • Timeframe of response
Adherence/patient behavior
<ul style="list-style-type: none"> • Frequency of treatment application • Topical formulation • Use of multiple topical therapies • Fast onset of action • Corticosteroid phobia • Tachyphylaxis • Long-term psychological burden of chronic treatment
Cost
<ul style="list-style-type: none"> • Multiple treatments vs combination formulations
Difficult-to-treat areas
<ul style="list-style-type: none"> • Individualizing treatment strategies for area of the body affected

required. We also aim to provide expert opinion to guide clinical practice on the long-term use of topical therapies. With that in mind, the following will also be addressed:

- The need for consensus on the terminology used for discussing long-term topical management of psoriasis, including different management strategies, e.g. on demand, tapering, proactive etc.
- An overview of existing long-term clinical data and discussion on how these data, in addition to the soon-to-report PSO-LONG study, may inform long-term management of psoriasis. PSO-LONG is a Phase III trial comparing the efficacy and safety of calcipotriol and betamethasone dipropionate (Cal/BD) foam with foam vehicle as part of a proactive long-term management regimen in patients with psoriasis.
- The current unmet needs in clinical practice, as well as discussion of potential solutions.

In the interests of brevity, this manuscript focuses on the use of topical treatments for the treatment of psoriasis in the absence of psoriatic arthritis, but, when establishing treatment regimens in clinical practice, topicals should be considered in the wider context of available therapies. In particular, the use of phototherapy (either whole body or targeted) has an overlapping indication with topical treatment which should be considered when devising an initial treatment plan. Although phototherapy is contraindicated for long-term or maintenance use, it can be an effective means of achieving remission (4,13), and thereby a potential consideration in combination with topical therapy for mild-to-moderate psoriasis. In addition, concomitant treatment with topicals is needed to treat plaques in UV shielded body areas.

Methodology

A panel of eight global dermatology experts (the authors of this publication) convened to discuss the current unmet medical needs in the long-term use of topical therapies for mild-to-moderate psoriasis. Each unmet need was explored further in order to identify potential areas for education for dermatologists. The experts discussed their opinions and agreed to capture these in a manuscript with the aim of guiding the long-term use of topical therapies in clinical practice for the management of psoriasis. The key considerations for long-term use of topical therapies for mild-to-moderate psoriasis included in this manuscript are

summarized in Table 1. The final content has been agreed upon by all authors.

Alignment on terminology for long-term management

One of the key problems we identified is that the terminology and the corresponding definitions used in the literature and clinical practice are confusing and alignment is required to reduce confusion and the potential for conflicting information. As an example, dermatologists may refer to 'long-term management', 'long-term maintenance' and 'long-term treatment' interchangeably.

'Long-term management' infers a holistic management strategy, as opposed to just treating for a longer time, and may include stress reduction and changes in lifestyle to achieve skin clearance. Basic treatment, intermittent use of drugs and adjunctive therapy also fall under long-term management. Long-term management strategies with topical therapies may include using reduced dosing and frequency of the induction treatment as a preventative measure. For example, dermatologists could consider applying topical therapies on two specified days of the week, as agreed in collaboration with the patient, e.g. weekends (15). Considerations for long-term management include the benefit/risk ratio, e.g. how much product should be used, which strength and for how long before a risk of adverse effects (16).

'Long-term treatment' infers treating in a continuous manner, or for a long time, and may additionally suggest that remaining relapse-free is difficult and requires intensive therapy. Whereas 'long-term maintenance' refers to the disease state in which remission has been obtained by the induction of treatment and maintenance treatment is employed to maintain remission and prevent relapses. This refers to a precise regimen according to signs and symptoms of disease. A maintenance regimen should allow for flexibility in intensifying or decreasing frequency of application of topical treatment, for example, with a less potent corticosteroid or vitamin D analog following remission with a strong corticosteroid or vitamin D/corticosteroid combination or continued use of a product on a less frequent basis.

We consider 'long-term management' to most accurately define the overall long-term strategy and is our preferred term and the one that will be used throughout this paper.

Other commonly used terms are also defined in Table 2 to provide further clarity, for example, the definition of 'relapse-free' and 'flare'. Table 3 also includes definitions of common tools used in clinical practice to measure disease severity such as Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA). There can be a lack of consistency and aligned terminology with the use of these tools in recommendations, so it is important to understand the differences. For example, the European guidelines (17) use PASI 75 (75% improvement in PASI), although PASI 90 is becoming a new therapeutic standard (18), while a Canadian expert opinion paper recommends the use of PGA (19).

Regarding long-term management with topicals, there are several different approaches to treatment regimens currently used:

- On demand/as needed: use continuously, for a specified number of days/weeks, until clear/almost clear and then switch completely to 'as needed', during which time the patient can retreatreat with the occurrence of symptoms.
- Tapering: treat continuously (e.g. daily) for a specified number of days/weeks, followed by gradual tapering by increasing the treatment interval or by decreasing the potency of

Table 2. Commonly used terms in psoriasis.

Terminology	Definition
Flare or reoccurrence	A period with breakout of active disease
Long-term management (preferred term)	Infers a holistic management strategy as opposed to just treating for a longer time
Long-term treatment	Infers treating for a long time and may additionally suggest that remaining relapse-free is difficult and requires continuous therapy
Maintenance treatment	Ongoing use of treatment at minimum frequency required to maintain control of the psoriasis and reduce the chance of flare
Proactive management	Use of intensive topical anti-inflammatory therapy until clearance of visible lesions, followed by less frequent application of low-dose anti-inflammatory agents to previously affected areas to prevent flares
Rebound	Following cessation of treatment, disease returns with greater severity than before treatment was initiated
Relapse-free	No recurrence of disease to the intensity prior to treatment, does not necessarily mean symptom-free
Symptom-free	Time during which patients are free of psoriasis symptoms
Tachyphylaxis	Decreasing response to treatment after multiple doses
Treatment goal	A pre-defined treatment objective, e.g. PASI 90

PASI 90: 90% improvement in Psoriasis Area and Severity Index.

Table 3. Commonly used clinical tools in psoriasis.

Clinical tools	Definition
BSA	A commonly used measure of psoriasis severity based on the percentage of the total body surface area affected by psoriasis
DLQI	Patient-reported tool used to assess the impact of skin disease on health-related quality of life and daily activities
PASI	An index used to express the severity of psoriasis by combining the severity of psoriasis (erythema, induration and desquamation) and percentage of affected area
PGA	A 5- or 6-point scoring system used to assess psoriasis severity (redness and induration), ranging from clear skin to severe psoriasis

BSA: body surface area; DLQI: Dermatology Life Quality Index; PGA: Physician's Global Assessment; PASI: Psoriasis Area and Severity Index.

treatment; for example, every second day for 2 weeks, then twice a week for 2 weeks, once a week for 2 weeks, and then pause the treatment. If the psoriasis activity increases at any stage, cease tapering and establish an appropriate interval at which the disease is at an acceptable level of activity (4).

- Preventative (proactive) applications: application of anti-inflammatory agents once or twice a week to previously affected areas to prevent flares (20,21).
- Treat-to-target: has its origins in rheumatology and is used primarily in the context of systemic therapies. This refers to the modification of treatment, as appropriate, until a defined objective/treatment goal has been achieved (17,22).

Proactive long-term management (up to 12 months) is well established for atopic dermatitis with the use of topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus. Although approved for the treatment of atopic dermatitis, TCIs are not approved for psoriasis. However, they are often used off-label for psoriasis in sensitive areas, such as the groin, genital area and on the face (16), and long-term management strategies with TCIs in atopic dermatitis may provide rationale and support for similar approaches in psoriasis. TCIs are not associated with skin atrophy or increased percutaneous absorption after prolonged use and have much lower potential for systemic effects (23,24).

Treatment goals in the context of long-term management

The goal of treatment is usually to achieve clear, or almost clear, skin with minimal signs and symptoms of disease (PGA 0/1),

with no adverse impact on patient quality of life (Dermatology Life Quality Index [DLQI] 0/1) and minimal safety risks; or to maintain a level of psoriasis that does not affect daily living (22).

A clear understanding of treatment goals is required for the successful management of chronic disease. This is particularly true in psoriasis given the heterogeneity of the disease and response to treatment (25). Although individualized treatment goals are more commonly applied to severe disease and the use of systemic treatment, they may also provide useful targets in the implementation of topical treatment for patients with mild-to-moderate psoriasis. Well-defined treatment goals can provide physicians with the guidance they need to tailor optimal care for their patients and therefore prevent poor outcomes. It is important to consider the severity of disease, phase of treatment (induction/maintenance), timeframe of response (short term/long term) and patient perspectives when establishing treatment goals.

Achievement of PASI improvement of 90% or better (which correlates with clear or almost clear skin (26)) is considered treatment success in psoriasis by the European Medicines Agency (18). However, PASI is impractical for everyday clinical practice, and especially for mild-to-moderate psoriasis, because it is complicated to calculate, difficult to interpret, time consuming, and not accurate in mild-to-moderate psoriasis (27). PGA is a more practical tool for measuring the severity of psoriasis but may be of limited value as a stand-alone instrument because it does not assess the body surface area (BSA) affected. Likewise, BSA measures area affected but does not record lesion severity (28). PGA 0/1 and absolute PASI may, therefore, be more

relevant treatment goals than PASI 90 for topical treatment. A composite of PGA and BSA, $\text{PGA} \times \text{BSA}$, has also recently been proposed for psoriasis assessments as a more practical tool than PASI. $\text{PGA} \times \text{BSA}$ has demonstrated a strong correlation with PASI and sensitivity in assessing disease severity and response to therapy (28,29). The DLQI is a validated patient-reported instrument used to assess the impact of skin disease on health-related quality of life and daily activities (30). Although DLQI is used routinely, it can be unreliable for everyday clinical practice as some questions are not applicable in all cases and this is particularly relevant to patients with mild-to-moderate disease. This expert panel recommends that PGA 0 or 1 (clear or almost clear) and/or DLQI 0 or 1 would be an optimal treatment goal for patients with mild-to-moderate psoriasis.

Current evidence: expert opinion, recent and ongoing clinical studies and real-world experience of long-term management

Expert opinion

Expert opinion increasingly supports the long-term topical management of mild-to-moderate psoriasis despite the absence of guidelines and recommendations. Some key publications of expert opinion and consensus are discussed below.

According to a recent consensus conducted in Asia on the management of mild-to-moderate plaque psoriasis with topical therapy, satisfactory control of the disease and prevention of relapses should be achieved during the maintenance phase with twice-a-week or weekend applications of a topical steroid, vitamin D analog or a fixed-dose combination of both. The fixed-dose combination is the preferred topical medication for both initial and maintenance phases of treatment (12). A panel of expert dermatologists in France recommended a similar approach with twice-weekly application of a combination of a vitamin D analog and a topical steroid as maintenance treatment on the lesion site in the context of limited data on maintenance strategies (13). The European consensus also supports topical long-term therapy with two-compound products (i.e. dual combination treatments, for example, Cal/BD) but either once or twice a week after initial therapy. This recommendation is based on the favorable risk-benefit ratio in maintenance trials and better cost-effectiveness (14).

In the UK and German guidelines, maintenance therapy with topicals is recommended but frequency of application is not specified. The NICE guidelines state that in those patients whose psoriasis is responding to topical treatment, after the initial treatment period, topical agents can be used when needed to maintain satisfactory disease control (8). The German guidelines for the treatment of psoriasis recommend topical maintenance therapy with corticosteroids, tazarotene or vitamin D3 derivatives, based on safety and tolerability profile and cost (4).

Evidence from clinical trials

There are few published studies/randomized controlled trials (RCTs) that have investigated long-term use of topicals and there is a lack of long-term (>6 months) maintenance studies. Indeed, a recent summary of a Cochrane systematic review on topical treatments for scalp psoriasis concluded that most findings were limited to short-term treatments (<6 months) and

that long-term assessments are needed (6–12 months) (31). The findings from some key RCTs are summarized in this section.

In a 12-week multicenter study evaluating the efficacy and tolerability of Cal/BD gel applied to scalp psoriasis following complete remission, maintenance of twice-weekly application of Cal/BD gel was found to be more effective and was associated with a lower rate of relapse versus on-demand treatment (32). Furthermore, adjunctive therapy with Cal/BD foam was associated with an improvement of every measure of disease activity (e.g. PGA; BSA) in a prospective, open-label study of psoriasis patients with an inadequate response to biologic therapy. This effect was maintained throughout the study in which all patients received once-daily Cal/BD foam for 4 weeks, followed by twice-weekly use on consecutive days for 12 weeks ('maintenance regimen'). The majority of patients achieved treat-to-target goals (33).

The PRO-Long study was a long-term, observational analysis in which 328 patients applied either Cal/BD gel ($n=152$) or Cal/BD body ointment ($n=176$) once daily for up to 52 weeks. At Weeks 24 and 36, there was a significant increase in the proportion of patients with 'mild' or 'very mild' disease from baseline (according to patient's global assessment of disease severity, PaGA), and this was sustained until Week 52. Although both formulations had comparable efficacy (Week 52: gel 13.1% increase vs ointment 16.4% increase), patients reported greater treatment satisfaction with the gel, which was considered easier to use, faster to apply and overall a more convenient product (34).

A retrospective, observational cohort study characterized pathways of psoriasis treatment over 3 years for newly diagnosed patients ($n=6875$) initially treated with a topical medication, and found that maintaining patients on an effective topical treatment can help to abate the need for a switch to oral treatments and biologics (35). Similarly, an observational retrospective analysis conducted in two Italian local health units reported that the use of fixed-combination topical treatment can improve patient adherence to treatment and decrease the likelihood of switching to biologic treatment (36).

The Topical Treatment Optimization Program (TTOP) was designed to improve adherence to treatment in psoriasis. In the large European investigator-initiated study, PSO-TOP, patients with mild-to-moderate psoriasis who had already failed previous topical therapy received Cal/BD gel as standardized study medication and were randomized 1:1 to either TTOP or non-TTOP management. TTOP management was provided *via* a five-element tool consisting of guidance for the conversation between dermatologists/nurses and patients, patient information material, telephone/e-mail helpdesks and treatment reminders. Cal/BD gel was applied once daily for 8 weeks followed by 'as needed' application for an additional 56 weeks. After 8 weeks of therapy, significantly more patients achieved a PGA of 'clear' or 'almost clear' in the TTOP arm than those in the non-TTOP arm (36.3% vs 31.3%, $p < .05$). This difference is expected to increase over time but the clinical relevance of these data remains to be determined. PGA responder rates remained higher in the TTOP group, although response rates in both groups remained >25% during the 'as needed' longer-term period (Week 8 to Week 64). Patients ranked the one-to-one conversations with the dermatologist or nurse as being the most important element of the TTOP (37). These findings support the importance of interactions between patients and healthcare professionals.

Table 4. Key PSO-LONG study details.

Study design	12-month, international, multicenter, randomized, vehicle-controlled, double-blind, two-arm, parallel group trial
Objective	To evaluate the efficacy and safety of a twice-weekly maintenance regimen with Cal/BD foam compared with vehicle in the prevention of relapse in subjects with psoriasis vulgaris
Key inclusion criteria	<ul style="list-style-type: none"> • A clinical diagnosis of psoriasis vulgaris for at least 6 months involving the trunk and/or limbs, amenable to treatment with maximum of 100 g of trial medication per week • Psoriasis vulgaris on the trunk and/or limbs (excluding psoriasis on the genitals and skin folds) involving • 2–30% BSA • PGA of at least ‘mild’ on trunk and limbs at Visit 1 • A mPASI score of at least 2 at Visit 1
Study completion	June 2019
Primary efficacy endpoint	Time to first relapse (at least ‘mild’ according to the PGA)
Secondary efficacy endpoints	<ul style="list-style-type: none"> • Number of days in remission (‘clear’ or ‘almost clear’ according to the PGA) • Number of relapses during the maintenance phase
Patient-reported outcomes	<ul style="list-style-type: none"> • DLQI • Adverse events associated with long-term corticosteroid use • Incidence of rebound • Local safety and tolerability • ACTH-Challenge test • Clinical laboratory evaluation to include albumin-corrected serum calcium levels
Safety outcomes	

ACTH: adrenocorticotropic hormone; BSA: body surface area; DLQI: Dermatology Life Quality Index; PGA: Physician’s Global Assessment; mPASI: modified Psoriasis Area and Severity Index.

Ongoing/recently completed RCTs

There are few ongoing RCTs investigating the use of topicals for the long-term management of psoriasis and the results are eagerly awaited—two ongoing RCTs are summarized in this section.

The Body Psoriasis: Long-term Relapse CONTROL (PSO-CONTROL) is a non-interventional study of real-life clinical practice strategies for long-term relapse control in patients with psoriasis, which plans to enroll 650 adult patients from 60–100 Russian dermatology sites and follow patients for up to 52 weeks with a focus on patients’ and dermatologists’ experience with the different topicals used (NCT03402828; primary completion date: January 2020) (38).

A randomized clinical trial with Cal/BD foam was initiated to examine a proactive long-term management approach for plaque psoriasis and to address some of the associated unmet needs and challenges in psoriasis (PSO-LONG; NCT02899962; study completion date: June 2019) (39). The PSO-LONG study is a Phase III trial comparing the efficacy and safety of Cal/BD foam with the foam vehicle used twice weekly as long-term maintenance therapy in patients with plaque psoriasis (Table 4). The primary outcome is time to first relapse, with secondary outcomes of number of days in remission during maintenance and the number of relapses during the maintenance phase.

Real-world experience

Alongside the data obtained from RCTs, there is growing interest in real-world experience (RWE) to facilitate more patient-centered approaches to treatment. Importantly, RWE studies (often in the setting of a registry) can provide additional value because they are conducted with daily-practice patients and treatment strategies that differ markedly from the strict conditions of RCTs (40). However, registries are generally designed to capture the use of systemic treatments so are of limited value in generating RWE for topical treatments.

RWE was recently obtained for use of Cal/BD foam in psoriasis from a German, multicenter, non-interventional, 4-week study, which reported convincing efficacy and tolerability in daily practice (41); however, longer-term data are generally lacking.

Additional long-term RWE data are needed to determine whether the efficacy observed with topicals in everyday clinical practice can be maintained beyond initial treatment. The ongoing Phase IV PSO-REAL trial is currently assessing the use of Cal/BD foam in everyday clinical practice over 1 year (NCT02935582; estimated completion date: December 2023) (42).

Key unmet needs in clinical practice for long-term management of psoriasis with topical treatment

The clinical outcomes and success of long-term management of psoriasis depend on factors such as treatment regimens, vehicle/formulation, patient treatment adherence, as well as important factors such as efficacy, methods used for response assessment and tolerability/safety (5). We considered the following key unmet needs in long-term topical management as the most pertinent to address.

Low patient adherence

In clinical practice, a barrier to successful topical treatment is patient non-adherence to therapy (5). Adherence to prescribed medication is fundamental to improving clinical outcomes (43). However, adherence rates to topical treatments are relatively low (50–70%) in patients with psoriasis (37,44) and are even lower (40%) for topical corticosteroids and in patients with severe disease (37). Furthermore, long-term adherence, which is crucial for the long-term management of psoriasis, is largely unexplored (45).

We identified the following factors as important drivers of adherence to prescribed therapies: frequency of treatment

application, treatment formulation, need for multiple therapies, fast onset of action, corticosteroid-phobia, long-term psychological burden of chronic treatment, low quality of life, topical fatigue and treatment goals.

It is important that treatment goals are agreed between the patient and physician to ensure ongoing patient adherence (46). Effective strategies that physicians can utilize to help patients achieve optimal therapeutic outcomes include positive patient-physician relationships, patient education, follow-up visits or calls, and patient participation in treatment decisions (47). Technology can also be a useful means of engaging with patients, for example, an app supporting psoriasis patients improved short-term adherence to topical treatment (48).

Lack of evidence regarding optimal frequency of treatment application

Once-daily treatment regimens are often preferred for induction therapy (49), with less frequent (once- or twice-weekly) application during maintenance treatment. Current German guidelines state that, if used for long-term management, calcipotriol should be given once or twice daily for up to 1 year; however, the guidelines acknowledge that the majority of evidence for the use of calcipotriol is short term (11). UK guidelines state that if once-daily topical preparations would improve adherence in those patients for whom twice-daily potent corticosteroids or coal tar preparations are indicated, a combined product containing calcipotriol and betamethasone dipropionate should be offered and applied once daily for up to 4 weeks (8). Topical long-term management with the application of two-compound products once or twice a week after initial therapy was recommended more recently in Germany (14).

Independent from recommendations and guidelines, less frequent (once- or twice-weekly) treatment application regimens are supported by physicians, as well as patients, and these regimens are crucial in the long-term management of mild-to-moderate psoriasis. The expert panel recommends a once-daily application regimen for induction and once or twice a week for maintenance.

Availability of new, more convenient and efficacious formulations

The formulation of topical therapies is an important consideration for patients when addressing long-term adherence to psoriasis topical care. New topical formulations with greater efficacy and more convenient application could promote adherence, leading to long-term maintenance of a disease-free state (3). Different formulations may also be more or less appropriate for use in different body parts, for example, gels, solutions, and foams are more appropriate for scalp psoriasis or hair bearing areas than ointments and creams (50). Reformulations of well-known active ingredients, e.g. betamethasone dipropionate, Cal/BD and clobetasol propionate, in the topical treatment of psoriasis have been associated with similar or improved clinical outcomes (51–53), as well as improved cosmetic acceptance, better tolerability and reduced frequency of application. The aerosol foam formulation of Cal/BD allows a state of supersaturation of the active substances (54), leading to increased skin penetration and local bioavailability in the skin compared with the ointment and gel formulations (55). Patient preference on formulation should be taken into consideration when prescribing a topical

therapy in order to meet their expectations and improve adherence (56).

Multiple topical therapies

The use of topical monotherapies that require separate applications is time consuming and can lead to poor treatment adherence (57); patients may prefer the simplicity and practicability of a fixed-dose combination regimen, which allows reduced frequency of application versus monotherapies (58). Examples of combination therapies include Cal/BD, betamethasone dipropionate/salicylic acid, diflucortolone/salicylic acid and tazarotene/halobetasol (59,60). The use of fixed-combination topical treatments can improve patient adherence to treatment (36). A Cochrane review has shown that use of a fixed combination of vitamin D/corticosteroid improves adherence compared with individual active components administered alone in patients with mild-to-moderate psoriasis (61). Furthermore, RWE suggests that combined treatment with vitamin D analog/corticosteroid therapy is preferred to single components used as monotherapies (62). Although some of these studies were not performed in the setting of long-term management, this expert panel believes that simplification of treatment is key for successful long-term management.

Corticosteroid phobia

Corticosteroids are often the topical treatment of choice. However, 'corticosteroid phobia', described as concern regarding the use of topical corticosteroids, is highly prevalent among dermatology patients, particularly atopic dermatitis, and often results in treatment non-adherence (63). Improved patient education and careful explanation regarding the appropriate use, safety and potency of topical corticosteroids is needed for overcoming non-adherence.

Indeed, potent-to-very-potent topical corticosteroids are not recommended for regular use over prolonged periods due to concerns over long-term adverse effects (7,8). In order to avoid steroid-induced adverse effects, vitamin D3 analogs, as monotherapy or combined treatment, are recommended for the topical long-term management of psoriasis (14,64); they can be used one or two times per week for maintenance dosing when used in combination with a low-potency topical steroid (64). Indeed, vitamin D analogs have been shown to decrease steroid-dependent skin atrophy *via* modulation of key extracellular matrix components (65).

Tachyphylaxis

Tachyphylaxis with long-term use of topical corticosteroids is a debated issue in psoriasis. Whilst there is evidence that topical corticosteroids do not lose efficacy with continued use (66–68), some healthcare professionals have concerns that patients can become tolerant to treatment. To help address these concerns, efficacy and safety data for long-term topical use are needed, as well as educational programs that counteract misinformation. Physicians and nurses are in a key position to directly influence a patient's perception of psoriasis and to clearly explain the importance of continuing treatment (5); it is also important that healthcare professionals work with patients to establish clear long-term treatment goals (46).

Cost

In addition to clinical aspects, economic factors determine topical long-term therapy (14). Psoriasis treatments can be very expensive; the costs of antipsoriatic treatments vary considerably from relatively cheap topical agents to highly expensive biological therapies (36). Use of multiple topical therapies can increase the overall cost so cost-effective options for long-term use are important.

A network meta-analysis performed in the UK assessed the cost-effectiveness of treatment sequences for psoriasis and demonstrated that potent corticosteroids were the most cost-effective treatment whether used alone or in combination with vitamin D for patients with psoriasis of the trunk and limbs. However, this study only modeled a 4-week treatment regimen (69). In a pharmacoeconomic analysis investigating the long-term use of vitamin D3 analogs in Germany, Augustin and colleagues used a Markov decision model and a simulated duration of 48 weeks, to demonstrate that daily use of a two-compound formulation of Cal/BD was significantly more cost-effective than daily treatment with both substances in monotherapy (total cost €571.33 vs €705.23) (14). Additionally, recent cost-effectiveness analysis using a Monte Carlo simulation demonstrated that Cal/BD in a fixed-dose combination foam is more cost-effective than standard of care for the topical treatment of mild-to-moderate psoriasis over 1 year (70).

Reimbursement policies also differ greatly between countries and this can impact the time allocated for consultations with patients. This can often result in reduced time available to provide sufficient education on appropriate topical treatment to support adherence.

Difficult-to-treat/important-to-treat areas

Notable difficult-to-treat areas include the scalp, face, intertriginous (including genitals), and palmoplantar regions. These pose a particular challenge to both physicians and patients despite the small surface area commonly affected by psoriasis in these locations (71,72). Psoriasis of the scalp, face, intertriginous areas, genitals, hands and feet may be underdiagnosed and/or undertreated and patients have disproportionate levels of physical impairment and emotional distress (72). As such, there is a need to individualize treatment strategies for psoriasis based on the area of the body that is affected and psoriasis subtype (72). Clinical trials assessing therapies for the difficult-to-treat areas have so far been inadequate but as understanding of the disease increases, this knowledge will help guide long-term management for these patients (71).

Discussion

Despite the majority of patients with psoriasis requiring topical treatment at some stage during their chronic, relapsing/remitting disease, there is a paucity of established guidelines on how to optimize long-term management of psoriasis with topicals. Furthermore, despite new innovative vehicles, the topical field has been long characterized by a lack of new treatments or strategies. This is in stark contrast with the field of systemic treatments. This expert opinion paper discusses the need for consensus on the terminology used in the field of psoriasis, with the adoption of 'long-term management' for the purposes of this manuscript. Regardless of nomenclature, a dearth

remains in clinical data surrounding the long-term use of topical treatments for management of psoriasis (particularly those with mild-to-moderate psoriasis). We have reviewed the guidelines and clinical data available, together with the unmet needs that still exist in clinical practice and provide our considerations for implementing long-term topical management in patients with psoriasis.

Although biologics have received much attention, they are not indicated for patients with mild disease (43) and traditional systemic therapies, which may be used in some cases, are also often discontinued due to safety/tolerability issues and lack/loss of efficacy (73). In contrast, topical treatment is widely available, less costly, not associated with serious safety issues, and empowers the patient to take control of the psoriatic disease without the need for specialized and expensive treatment (43).

Whilst data on long-term use of topical treatments are currently limited, long-term management should be considered mandatory to ensure patients receive appropriate proactive treatment which may help optimize adherence and long-term outcomes. It is vital to involve the patient in decisions around the topical management of their disease, particularly in the long term. Understanding a patient's concerns can help tailor conversations and enable the dermatologist to provide relevant information—all of which will help promote treatment adherence. In the future, long-term studies, such as the PSO-LONG study, will help inform long-term strategies for the management of psoriasis.

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