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CONFERENCE REPORT

Psoriasis: consensus on topical therapies

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Abstract

Objective A consensus conference was convened to evaluate the topical treatment of psoriasis.

Participants Members of the International Psoriasis Council (IPC) with broad clinical experience in the treatment of psoriasis and a specialist in meta- and pharmacoeconomic analyses were invited to participate on the consensus panel. Those accepting the invitation convened in Saariselkä, Finland.

Evidence An advisory group on topical treatments was nominated by the organizing panel members. All participants reported at the consensus conference on evidence based data with respect to disease severity assessment, the available data on efficacy and safety and on a comparative efficacy/safety analysis.

Consensus process At the consensus conference, the presentations were discussed and conclusions, which were reached by the group, were recorded. Active participants of the group wrote assigned sections of this consensus document with a majority of participants agreed on the conclusions.

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Introduction

Management of psoriasis comprises a large repertoire of topical, systemic treatments and photo(chemo)therapy. More recently, biological therapies have provided additional opportunities to the systemic treatment of psoriasis. Nonetheless, topical therapy remains the mainstay in the management of psoriasis; with multiple agents being available, a challenge remains to define patients eligibility for a topical treatment or systemic treatment. Likewise, severity assessment and improving compliance are important approaches to improve care for patients with psoriasis, as is the evaluation of efficacy and safety characteristics of individual topical therapies. Once the efficacy and safety characteristics are defined, it is possible to define a therapeutic ladder.

The International Psoriasis Council (IPC) is a not-for-profit collaboration of physicians working to advance psoriasis education, research and treatment. On February 10, 2006, in Lapland, Finland, IPC convened a 'roundtable' of international experts in the management of psoriasis with the objective of debating and agreeing on the optimal use of topical therapies to treat psoriasis. This meeting addressed the following questions:

1 Which factors determine treatment selection in individual patients, reconciling disease severity parameters and compliance?
2 Which topical treatments are available and what are their efficacy and safety characteristics?
3 Is it possible to define a therapeutic ladder based on the available evidence-based data?
4 In order to optimize the positioning of the available topical treatments, what further data are required?

The objectives of this consensus group were to assess the literature with regard to the safety and efficacy of topical therapies for the treatment of psoriasis, to evaluate deficiencies in the available literature and to establish guidelines for the use of topical therapies based upon the literature and clinical experience.

Methods

An organizing committee consisting of a chair and cochair invited candidates to participate in the consensus process and meeting. Candidates were identified by the organizing committee based upon membership in the IPC, experience in clinical investigations, recognition as clinicians with broad experience in the treatment of psoriasis, and recommendations of IPC councillors. Those accepting the invitation were polled to identify a participant specializing in meta- and pharmacoeconomic analyses.

Participants were assigned by the organizing committee to specific topics based upon therapeutic classes of topical therapies. Outcomes measures were similarly assigned to one participant. Participants were requested to review the relevant literature to highlight mechanisms of action, as well as safety and efficacy as determined by clinical studies, case reports, or otherwise as available. The paucity of data available for most commonly used topical therapies and the intent of the review: to provide a practical consensus directive for the topical treatment of psoriasis, precluded a complete, validated, evidence based assessment of the literature.

Participants presented summaries of their findings to the entire panel. Presentations were subject to questions and open debated. Contentious points were re-assessed and deliberated following the formal presentations. Those points for which unanimous consensus was not achieved are addressed in the discussion.

Severity assessment and compliance: outcome measures

The management of psoriasis requires an understanding of the complex issues involved in appropriate decisions on therapy and an appreciation for the often difficult target of achieving and maintaining treatment success. Severity of psoriasis has traditionally been determined by the physical extent of disease, disregarding the other components of the consultation: psychosocial disability/impairment of quality of life and previous response to treatment. Measures of physical extent of disease incorporate body surface area (BSA) affected by psoriasis. The psoriasis area severity index (PASI)[1] was developed in 1978 as a specific measure of psoriasis response to a new retinoid. It was never intended to be the 'gold standard' of clinical outcome but by default was incorporated into many clinical trials of new therapies. However, PASI is an advance on BSA in that it includes important clinically relevant parameters of psoriasis: erythema, scaling and plaque thickness. The PASI is calculated using a formula for average lesion severity modified by and area weighted measure applied to anatomical sites. The resultant score is 0 (no psoriasis) to a theoretical maximum of 72. Two limitations of the PASI are its non-linear area scoring and, theoretically, the increasingly sparse number of patients having high PASI scores. In clinical practice, it is uncommon to see a patient with PASI > 30. Furthermore, PASI is an insensitive measure of psoriasis of limited extent, when the area involved is less than 10% of the total body surface area. Other measures attempting to overcome the perceived limitations of the PASI include the Lattice Scale[2] and physicians' global assessment (PGA). An international development of one generally accepted scoring system is of importance as the current use of different scoring systems is a major complication in the comparison of treatment results obtained in different studies. In an attempt to capture the holistic components of the

consultation, the Salford Psoriasis Index (SPI) was developed.[3] SPI is a three integer scale similar to 'tumour; nodes; metastasis' for cancer which incorporates physical extent (signs) of psoriasis (S; 0–10 truncation of PASI); psychosocial disability (P; 0–10 on a visual analogue scale); and historical interventions (I; a cumulative score incorporating previous systemic therapies and length of use). Refinements to this approach have been adapted by the 'Rule of Tens' where 'severe psoriasis' is defined as a PASI ≥ 10 Dermatology Life Quality Index (DLQI) ≥ 10 and body surface area (BSA) ≥ 0.[4]

In reality, topical treatments may be used for psoriasis of any severity, with limitations based on patient compliance, patient specific needs and response to therapy. It is commonly accepted that a BSA of approximately ≤ 5% is amenable to and most appropriately treat using monotherapy with topical agents. Systemic absorption in patients with widespread psoriasis is another limitation. A key aspect of response to topical therapy is compliance or concordance with treatment. Studies addressing this have shown that up to 39% of psoriasis patients are self-admittedly non-compliant,[5] particularly those who have the most severe impairment of quality of life from their psoriasis. Not surprisingly, those patients who are least likely to comply with therapy are young, unemployed men. Compliance is optimal early in the course of treatment and more likely when topical agents are used once daily.[6,7] A small percentage of motivated patients with more widespread disease may comply with long-term topical therapy. In contrast, the majority of patients will seldom use topical agents twice daily on a maintenance basis.

Pharmacology, efficacy and safety of topical treatments Review of current topical agents

Dithranol and tar

Pharmacology

Dithranol (anthralin, cignolin) is 1,8-dihydroxy-9-anthrone. It induces a cascade of free radicals in the skin, resulting in antiproliferative effects and a modulation of inflammation in psoriasis. Interruption of adenosine triphosphate by damaging mitochondria may account for additional antiproliferative effects of dithranol.[8]

Coal tar is a by-product of the destructive carbonization and distillation of coal, roughly comprising 48% hydrocarbons, 42% carbon and 10% water. Coal tar has antiproliferative effects and, like dithranol, modulates inflammatory events in psoriasis.

In general, standardization of formulations of dithranol and coal tar products is poor.

Efficacy and safety of dithranol

Few placebo-controlled or head-to-head comparative studies are available to substantiate the efficacy and safety of this time-honoured treatment. Open studies, mostly retrospective, indicate clearance in 72% to 95% of the patients treated with dithranol 24-h applications. Shorter application times of dithranol (5–30 min) resulted in clearing in 10% to 72% of the patients. Home applications were less effective as compared to hospital, day care, or outpatient treatments (see for review, van de Kerkhof *et al.*)[9] Confounding these analyses and interpretation of treatment results were the frequent concomitant treatments (tar, topical corticosteroid and phototherapy). In an analysis of placebo-controlled studies and head to head comparisons, dithranol was suggested to have a low efficacy.[10]

Use of dithranol in hospital-based or day care clinics, whereas evidence is limited, can be a highly effective approach if concentration increments are carried out carefully, with or without additive phototherapy.

Short-term side-effects of dithranol are irritation (48–72 h after the application) and staining of the skin, nails and clothing. There is no evidence for long-term cutaneous or systemic toxicity.

Efficacy and safety of tar

Few placebo-controlled studies or studies against an active comparator are available for tar-based treatments. Although efficacy of sol. carbonis detergens 5% in petrolatum has been claimed to be superior compared with placebo,[11] head-to-head comparative studies against calcipotriol revealed that various tar preparations are less effective.[12–14]

Side-effects of tar include immediate and long-term effects. Messiness, staining and odour, irritant, allergic, and phototoxic responses, folliculitis and bronchoconstriction in asthmatic patients are the most important immediate side-effects. Although occupational exposure to coal tar is associated with an increased risk of lung, scrotal and skin cancer, carcinogenicity following coal tar applications in psoriatics and patients with atopic dermatitis remains unsubstantiated.[15–17] However, in PUVA-treated patients,[18] coal tar was implicated as an increased risk factor for carcinogenicity.

Corticosteroids

Pharmacology

Corticosteroid molecules bind to a high affinity glucocorticoid receptor, which, upon activation, separates

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from associated non-DNA binding proteins: dimerized heat shock protein 90, heat shock protein 70, and FKBP 52. Activated glucocorticoid receptors dimerize and passively transport across the nuclear membrane where the glucocorticoid-receptor dimer activates specific nuclear transcription elements, ultimately leading to biological response. The dimer may also impact nuclear factor-κB transcription elements. A wide range of biological responses from corticosteroids, favourable and unfavourable, have been identified, including direct effects on dendritic cell differentiation and function, lymphocyte apoptosis, toll-like receptor regulation, cytokine inhibition, collagenase and elastase expression.

Efficacy and safety

The clinical efficacy of corticosteroids as monotherapy for psoriasis is unquestioned; however, scientific validation remains incomplete. Although it is commonly accepted that rebound and tachyphylaxis occur with the respective withdrawal and continued use of topical corticosteroids, neither are well defined, neither are evaluated in rigorous clinical studies.

The limited number of well-controlled, blinded studies allows two conclusions regarding the efficacy of topical corticosteroids as monotherapy in psoriasis: intermediate potency corticosteroids have modest efficacy, whereas potent and ultra potent corticosteroids, recommended for only short-term (2-week) courses of therapy, have significant efficacy in the treatment of psoriasis.[19,20]

With respect to side-effects,[21–28] while two common concerns are frequently discussed, both are inadequately characterized:

I The rapid atypical recurrence of disease upon discontinuation of treatment: rebound.[29–31] Although rebound does occur with discontinuation of topical and systemic corticosteroids, the frequency and severity of such events have not been adequately studied.

II The progressive loss of efficacy upon continued use of corticosteroids: tachyphylaxis.[32] Tachyphylaxis was identified by du Vivier and Staughton[32] and recently reviewed by Feldman.[33] However, there remain inconsistent and sometimes conflicting reports regarding this important issue.[34,35]

In order to reduce the perception of an apparent reduced efficacy with continuous use of potent topical corticosteroids, numerous innovative techniques are used by clinicians, including 'weekend only' steroid usage, combination with non-steroid products such as calcipotriol or tazarotene.

Tazarotene

Pharmacology

Tazarotene is a synthetic acetylenic retinoid. This retinoid has a more selective affinity for the retinoic acid receptor (RAR) than tretinoin. Tazarotene shows transactivation through RAR-γ and RAR-β and less through RAR-α; furthermore, it does not bind to retinoid X receptor (RXR). Tazarotene has been shown to have antiproliferative and anti-inflammatory activities. Teratogenic aspects of topical tazarotene are only of concern if greater than 20% of the body surface is treated.

Tazarotene (0.05% or 0.1%) is available as gel and cream formulations.

Efficacy and safety

In two multicentre placebo-controlled studies, efficacy and safety of tazarotene gel and cream have been shown for short-term use during 12 weeks.[36,37] A positive feature of tazarotene is its ability to maintain clinical response after discontinuation of treatment. Clinical response was assessed by reduction in plaque thickeness, erythema and scaling. In these studies, the success rate was defined as the percentage of patients reaching at least a moderate 'global response 'or better. After 12 weeks treatment, 49% to 59% of patients treated with tazarotene 0.1% cream had reached this response, vs. 42% to 48% of patients treated with tazarotene 0.05% cream and 30% to 37% of patients treated with the vehicle only.

The most important concern relating to topical tazarotene treatment, in addition to its teratogenicity potential, relates to treatment-related adverse events (i.e. pruritis, erythema, burning and desquamation within and especially peripheral to the lesion seen in a significant proportion of patients). This may be moderated by applying the Tazarotene in conjunction with topical corticosteroids.

Vitamin D analogues

Pharmacology

Vitamin D analogues bind to the vitamin D receptor (VDR) and, following dimer formation with members of the nuclear receptor super family, VDR binds to vitamin D response elements (VDREs), resulting in activation of genes involved in epidermal proliferation, inflammation and keratinization.

At present, three vitamin D analogues are available in Europe for the treatment of psoriasis: calcitriol, tacalcitol and calcipotriol, with only calcipotriol available in the USA.

Efficacy and safety of vitamin D_3 analogues as monotherapy

Calcitriol

Calcitriol (Silkis®) is the hormonally active form of vitamin D. At a dose of 3 μg/g, calcitriol ointment applied twice daily is superior to placebo for the treatment of psoriasis affecting the trunk and limbs.[38]

Assessment of the systemic safety of calcitriol ointment 3 μg/g in an open-label study showed no change of calcium homeostasis in psoriatic patients with 5% to 35% body surface involvement.[39] In addition, calcitriol ointment was safe and well tolerated in open-label long-term studies.[40] In 253 patients treated for up to 78 weeks, no clinically relevant changes in measures of calcium homeostasis were detected.

Compared with betamethasone dipropionate, treatment with calcitriol for 6 weeks produces similar improvement.[41] In this randomised, multicentre trial including 258 patients, improvement was recorded in 79% and 82% of patients receiving calcitriol or betamethasone, respectively. Evaluation post-therapy for 8 weeks revealed that fewer patients required re-institution of treatment in the calcitriol group than those discontinuing betamethasone dipropionate therapy.

Treatment with calcitriol ointment is effective and safe for the short-term treatment of chronic psoriasis. Treatment may be continued according to clinical need, although long-term efficacy and safety is only established in open-label treatment applied intermittently for 1 year.

Tacalcitol

Tacalcitol (Curatoderm®, Apsor®) is a synthetic vitamin D_3 analogue. Tacalcitol ointment 4 μg/g applied once daily is superior to placebo.[42–44] Improvement was better for tacalcitol (44%) compared with vehicle (26%). In safety studies, hypercalcemia was not observed during tacalcitol therapy.[45] Tacalcitol ointment 4 μg/g is well tolerated in sensitive skin areas.[45] Long-term efficacy and safety have been reported in an open-label study.[46] In 197 patients, the median PASI fell from 9.5 to 4.6 at months 3 and 3.25 at months 18. There were no clinically relevant changes of calcium homeostasis.[44] Treatment with tacalcitol ointment 4 μg/g is less efficacious than potent steroids.[44,45] Formulated in an emulsion, tacalcitol 4 μg/g once daily is efficacious, safe and well tolerated for the treatment of scalp psoriasis.[47]

Treatment with tacalcitol ointment is effective and safe for short-term therapy of chronic psoriasis. Treatment may be continued, although long-term efficacy and safety is only established in open-label, intermittent treatment for 1 year.

Calcipotriol

Calcipotriol, or calcipotriene in the USA, is a synthetic vitamin D_3 analogue with a low calcemic effect. It is the most extensively studied vitamin D_3 analogue for psoriasis. Calcipotriol ointment and cream 50 μg/g are marketed for the treatment of plaque-type psoriasis vulgaris under the trade names Daivonex®, Dovonex® and Psorcutan®. Treatment with calcipotriol concentration induces a marked improvement in about two thirds of the patients after 8 weeks.[48] The efficacy and safety of calcipotriol ointment 50 μg/g has been confirmed in a twice-daily regimen multicentre, double-blind, placebo-controlled, right-left study[49] and in a once-daily regimen in a double-blind, multicentre, placebo-controlled study.[50]

Treatment with calcipotriol is safe at a dose up to 100 g per week as recommended in the current license. The efficacy of calcipotriol has been compared with a number of potent and ultrapotent corticosteroids.[51–53] Short-term therapy with calcipotriol is at least as effective as potent corticosteroids, but less effective than ultra potent corticosteroid.

Calcipotriol ointment or cream applied once or twice daily is effective for short-term therapy of chronic plaque psoriasis. Treatment is frequently continued on a maintenance basis, although long-term efficacy and safety is only established in open-label, intermittent therapy for 1 year.

Two-compound product of calcipotriol and betamethasone

The two-compound product containing calcipotriol 50 μg/g plus betamethasone dipropionate 0.5 mg/g is marketed as Dovobet®, Daivobet® and Taclonex®. Six large, randomised trials have assessed the efficacy of calcipotriol/betamethasone dipropionate in adults with psoriasis vulgaris.[54–59] Five were double-blind trials; calcipotriol/betamethasone dipropionate once or twice daily for up to 4 weeks improved the PASI by 65.0% to 74.4% from mean baseline scores of 9.5 to 10.9. This was significantly better than seen with placebo or once- or twice-daily monotherapy with the individual ingredients calcipotriol, betamethasone dipropionate and tacalcitol (comparators varied between trials, but all differences were significant). There was no significant statistical difference between once- and twice-daily calcipotriol/betamethasone dipropionate. Lesional/perilesional drug reactions (most commonly pruritus) occurred in up to 10.6% of recipients

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of calcipotriol/betamethasone dipropionate, with no significant difference between once- and twice-daily administration. This was significantly better than with calcipotriol, similar to betamethasone dipropionate, and, in one trial, significantly better than placebo. Furthermore, the combination product applied once daily was superior to calcipotriol applied twice daily in terms of reduction in quality of life measures.[60]

The safety of maintenance therapy with the calcipotriol/betamethasone two-compound product was evaluated in 52-week randomised, double-blind study, where 634 received either 52 weeks of two-compound product, 52 weeks of alternating 4-week periods of two-compound product and calcipotriol, or 4 weeks of two-compound product followed by 48 weeks of calcipotriol.[61] Treatment in all groups was used once daily when required. Adverse drug reactions commonly associated with long-term topical corticosteroid use occurred in 4.8% of patients in the two-compound group, 2.8% in the alternating group and 2.9% in the calcipotriol group. Statistically, there was no difference between the three treatment groups. Thus, the two-compound seems to be safe and well tolerated whether used on its own for 52 weeks or alternating every 4 weeks with calcipotriol.[62]

Comparative efficacy and tolerability of vitamin D_3 analogs

For short-term therapy calcipotriol was more effective than calcitriol[62] and tacalcitol.[63] No differences in adverse events or withdrawal were found. This is despite the higher frequency of skin irritation reported for calcipotriol in non-comparative studies. Combination therapy with a group III steroid and calcipotriol is more effective than calcipotriol alone. This is also the case for a two-compound product of calcipotriol and betamethasone dipropionate. The fixed combination has to date not been compared with polytherapy consisting of its active ingredients. However, it offers the advantage of once daily application.[53–58]

A review of the literature on maintenance therapy with vitamin D_3 analogs reveals only a single double-blind controlled study. In this study, the fixed combination of calcipotriol and betamethasone dipropionate proved to be safe and well tolerated.[61] In conclusion, calcipotriol is more effective than the other vitamin D_3 analogs for short-term therapy of chronic psoriasis. Vitamin D_3 analogs may cause skin irritation when used as monotherapy. Addition of topical corticosteroid to vitamin D_3 therapy results in improved short-term efficacy. Scientific evidence is strongest for the single two-compound product of calcipotriol and betamethasone dipropionate used once daily, with safety demonstrated over a 52-week study period in a large number of subjects in several well-controlled, blinded clinical studies.

Calcineurin inhibitors

Pharmacology

Calcineurin inhibitors developed for the topical treatment of atopic dermatitis include Tacrolimus and Pimecrolimus. Calcineurin inhibitors are macrolide immunosuppressant and inhibit T-cell activation via inhibition of dephosphorylation of cellular NF-AT (nuclear factor of activated T cell). Tacrolimus 0.03% and 0.1% and pimecrolimus 1.0% have been shown to be effective in atopic dermatitis.

Efficacy and safety

I. Chronic plaque psoriasis

Several studies have shown limited efficacy of pimecrolimus (0.3% or 1.0% cream) and Tacrolimus (0.3% ointment) in psoriasis unless applied under occlusion. Efficacy of Tacrolimus under occlusion was superior to calcipotriol and less effective than clobetasol 17 propionate.[64–66] However, without occlusion the severity score was only reduced by 33% vs. 42.9% with placebo.[67] Pimecrolimus 1% + urea 10% ointment proved to be better than vehicle but worse than calcipotriol ointment.[68] Addition of salicylic acid 6% gel to Tacrolimus 0.1% ointment resulted in at least 'marked improvement' in 46% of the patients vs. 17% of the with salicylic acid as monotherapy.[69] Calcineurin inhibitors without occlusion or 'penetration enhancers' are not effective in chronic plaque psoriasis outside of face and flexures. In combination with penetration enhancers, their efficacy approaches that of calcipotriol, however, at the expense of considerable irritation.

II. Flexural and facial psoriasis

In flexural and facial psoriasis, Tacrolimus 0.1% ointment and pimecrolimus 1% cream have been shown to be effective and well-tolerated in randomized double-blind, placebo-controlled studies. Lebwohl *et al*. showed marked improvement in 66.7% of patients with facial and flexural psoriasis against 36.8% of patients with the vehicle only.[70] In flexural psoriasis, pimecrolimus cream resulted in such improvement in 71% of the patients against 20.7% of the patients treated with the vehicle only.[71] Several open studies and case reports confirm these results and suggest efficacy and safety in psoriasis of sensitive sites in children and elderly. In conclusion, while currently available calcineurin inhibitor preparations show efficacy for flexural and facial forms of psoriasis

only, they are not currently licensed for the treatment of psoriasis.

Combination treatments

Coal tar and dithranol

Coal tar and dithranol can be combined with all antipsoriatic treatments.

In particular, the combination with ultraviolet B treatment and, to a lesser degree, topical corticosteroids, are time-honoured principles. However, well-designed placebo-controlled, prospective studies of these combination treatments are sparse with recent studies suggesting that these combinations have little therapeutic value.[72–77]

Tazarotene

Combination of tazarotene with topical corticosteroids and UVB proved to be more effective and safe compared with monotherapies. In addition, the combination of tazarotene formulations with topical corticosteroid preparations proved to be an important combination, improving efficacy, while reducing irritation and the atrophogenic potential of topical corticosteroids.[78,79] A 1998 study showed a statistically significant improvement using either mid or high-potency topical steroids in combination with tazarotene, with a trend towards a lower incidence of treatment-related adverse events noted in these two groups vs. tazarotene and placebo and tazarotene and low-potency topical steroids.[80] A further study published in 2001 evaluated the efficacy and safety of a tazarotene gel (TG) with an initial phase of clobetasol propionate 0.05% ointment.[78] Utilizing clobetasol at night and tazarotene in the morning for the first 2 weeks, with slow tapering of clobetasol over the ensuing 4 weeks to twice weekly, while maintaining tazarotene thrice weekly, resulted in a significant clinical response. Thereafter, in the post-treatment phase, clinical response was maintained in 73% of patients maintained on TG thrice weekly and twice weekly clobetasol regimen, again with a significant decrease in irritancy.

Vitamin D_3 analogues

Combinations of calcipotriol with many topical treatments, photo(chemo)therapy and classical systemic treatments have been studied in randomized controlled studies. In particular, the combination of calcipotriol with topical corticosteroids has been shown to enhance efficacy and reduce side-effects.[53–60] The addition of calcipotriol to photo(chemo)therapy and to systemic treatments has been shown to reduce cumulative doses of UV radiation and systemic treatments.[81–85] A two compound formulation is available of calcipotriol and betamethasone dipropionate (Dovobet®, Daivobet®, Tacrolex®; see above). Calcipotriol, in controlled studies, has been shown to increase the efficacy/safety ratio of photo(chemo)therapy,[81,82] methotrexate, cyclosporine and acitretin.[83–85]

Calcineurin inhibitors

To date, no studies are available on the combination of calcineurin inhibitors and other antipsoriatic treatments.

Current data limitations for evaluating and optimizing the topical treatment of psoriasis

Evidence-based data on short-term efficacy and safety of available topical treatments are highly fragmentary. Whereas efficacy and safety of calcipotriol as monotherapy and in combination treatments, especially for short-term interventions, is supported by placebo-controlled studies and head-to-head comparisons, evidence-based information on all the other treatments is limited despite their prolific use by dermatologists worldwide. It is essential that more thorough, scientific data on safety and efficacy are obtained for all topical treatments of psoriasis. Appropriate head-to-head comparisons are required to support appropriate evidence-based treatment guidelines for the topical therapy of psoriasis, short-term and longer-term.

With respect to long-term studies, scientific evidence on calcipotriol and the two-compound product calcipotriol-betamethasone dipropionate is superior to that on other topical treatments. In a lifelong disease like psoriasis, it is important to maintain clinical efficacy with minimal side-effects. Although the combination of vitamin D_3 and corticosteroids is a common approach, our information on the combination of topicals with systemic treatments is restricted to calcipotriol. There is scant information on the combination of other topical agents with systemic treatments, either non-biological or biological therapies.

Psoriasis involving the scalp, flexures, face and palms-soles is commonplace,[86] the scalp being the site most frequently affected. Evidence-based data on safety and efficacy of topicals on these special sites are lacking, thereby requiring dermatologists to use their best empirical skills to help the patient.

A profound lack of evidence-based data is noted in children and the elderly.

Perhaps the most important limitation to developing uniform treatment guidelines for the topical treatment of psoriasis is the potential variation in response to antipsoriatic treatments: long-term, head-to-head studies with well-defined, empirically relevant clinical outcomes are

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absent. It is difficult to understand why patients with virtually the same clinical morphology and the same objective severity scores of psoriasis may have highly different responses to individual agents: as noted by most participants but unsupported by the literature. A full understanding of the heterogeneity with respect to pharmacokinetics and pharmacodynamics is a challenge to dermatologists as we seek to optimize our treatments. It is hoped that pharmacogenomics and well-designed studies will provide important new research opportunities to address these issues.

Conclusion

There is currently no universally accepted measurement of psoriasis severity adequate for use by dermatologists in their routine disease severity assessment of psoriasis though the PASI remains the most commonly used in controlled studies. Disease severity in clinical studies and ideally in clinical practice should comprise a physical score, a quality of life score, and a patient satisfaction index. We are hopeful that ongoing investigation and evaluation of scoring systems will result in robust, applicable and accepted measures. Furthermore, responses to previous treatments could supplement severity assessments by indicating recalcitrant disease before selecting a specific treatment for a patient. It was agreed by most authors that a holistic score for routine use should be simple and reconcile the individual phenotype, including special sites such as face, flexures, scalp, and palms and soles. Even patients with widespread extensive psoriasis may be effectively treated with a topical therapies, provided adequate time for education is given the patient to enhance compliance and appropriate use.

Data in support of efficacy for most topical agents are sorely lacking. As a consequence, a treatment ladder could only be defined using clinical experience for guidance. Evidence for efficacy and safety is limited to dithranol, tar, corticosteroids, vitamin D_3 analogues and calcineurin inhibitors. However, clinically rigorous assessments to the current standards of evidence-based medicine, including placebo-controlled studies and head-to-head comparative studies are largely restricted to vitamin D_3 analogues and ultrapotent corticosteroids. By far, the most extensive evidence-based data are available for the vitamin D_3 analogue calcipotriol and the two compound product of calcipotriol-betamethasone dipropionate. Therefore, it is not possible to define an appropriate therapeutic ladder from currently available evidence-based data. It can, however, be concluded that clobetasol-17-propionate, for short-term use, and the two compound product calcipotriol-betamethasone dipropionate, for short-term and longer-term use, are effective treatments based upon multiple, well-designed, well-controlled, randomised clinical trials. Furthermore, safety over 52 weeks has been shown in a large, appropriately designed study for the two compound product of calcipotriol and betamethasone dipropionate.

Psoriasis at sensitive sites (face and flexures) requires a different therapeutic approach due to the potential side-effect profile of corticosteroids and the irritancy potential of vitamin D_3 analogues, tazarotene and dithranol. Low-potency corticosteroids as monotherapy or in combination with other agents such as Vitamin D_3 analogues or anti-microbial agents are used for psoriasis in these sensitive sites. There are no controlled studies to support the latter. Calcineurin inhibitors, whereas effective when treating the face and intertriginous regions, are not indicated for the treatment of psoriasis and have proven ineffective when applied outside of the face and folds. Topical agents can be combined with each other, with phototherapy, systemic treatments and biological agents. Only the combination of vitamin D_3 and topical corticosteroids or tazarotene with a topical corticosteroid has been shown to be effective and safe. The two-compound product calcipotriol-betamethasone dipropionate used on a daily basis for 4 weeks and then intermittently as needed, has been shown to be more effective compared with each of the monotherapies used individually and proved to be safe during a 52-week treatment period.

Despite decades of clinical use, evidence-based data is sparse for the more classic topical treatments: tar, dithranol and topical corticosteroids. Long-term comparative studies are not available for the vast armamentarium of topical therapies for psoriasis. Evidence-based data on combination treatments other than vitamin D_3 combinations or tazarotene combinations are likewise not available and too fragmentary to base any specific recommendations on for the treatment of flexural, facial, scalp and palmoplantar psoriasis. Carefully designed study and the burgeoning field of pharmacogenomics and targeted therapy will likely facilitate treatment selection within the next decade.

In summary

1 A general Disease Severity Assessment (DSA) for psoriasis would facilitate a decision on whether an individual patient is eligible for a topical treatment.
2 DSA should comprise at least a physical score, a quality of life score and a potentially assessment of response to prior therapies.
3 The phenotype of psoriasis, including the anatomic localization (in particular face, flexures, scalp, palms and soles) should be reconciled.
4 There is in principal no cut-off point for any severity score, which excludes a patient for topical therapy.

In extensive psoriasis, compliance to treatment and maximally permitted quantity of the preparation may be limiting factors.

5 Tar and dithranol (anthralin) have inadequate controlled studies to draw any conclusions regarding efficacy, safety and tolerability. Only ultrapotent corticosteroids, tazarotene and vitamin D_3 analogues have controlled clinical studied showing them to be effective and safe treatmentss over the short-term. Head-to-head comparative studies have shown that calcipotriol in combination with betamethasone dipropionate is superior to either alone.

6 Long-term safety (at least 52 weeks) has been shown for vitamin D_3 derivates and the combined product calcipotriol-betamethasone dipropionate

7 For facial-flexural psoriasis low potency corticosteroids, vitamin D_3 analogues and calcineurin inhibitors are appropriate though only the latter have been studied.

8 Evidence-based data on combination treatments are restricted to vitamin D_3 analogues and tazarotene. The combination of these products with topical corticosteroids seems to enhance efficacy and reduce irritation.

9 Long-term comparative studies of topical treatments are not available but are needed for evidence-based long-term treatment strategies. Evidence-based data on therapeutic responses in different phenotypes of psoriasis and site-specific phenotypes (face, flexures, scalp, palms and soles) are rare. Evidence-based data on the treatment of psoriasis childhood and the elderly are profoundly scarce.

10 Variation between treatment responses of individual patients requires further studies.

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