Evidence and Suggested Therapeutic Approach in Psoriasis of Difficult-to-treat Areas: Palmoplantar Psoriasis, Nail Psoriasis, Scalp Psoriasis, and Intertriginous Psoriasis

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Introduction

Management of psoriasis is always difficult. Apart from being very notorious in showing frustrating therapeutic response in many cases, this has a natural tendency toward frequent relapse. Most of the systemic drugs that are used traditionally to treat this disease are known to have significant adverse effects on the body. Drug-related toxicity from these drugs is often cumulative for some drugs. Long-term safety data are lacking for most of the newer drugs like biologics. To add to this, there are some body areas that are even more resistant to treatment or are too sensitive to be treated with strong topical drugs necessitating systemic drugs more frequently in these locations.

This article has focused on the available evidence on the treatment of such difficult-to-treat areas such as palms-soles, scalp, nails, and intertriginous areas and suggested the most logical therapeutic recommendation in such conditions. This article has been prepared after reviewing extensively the published and one unpublished article searching three internationally accepted large database called PubMed, Embase, and Cochrane database. Inclusion criteria were published articles on the treatment of difficult-to-treat psoriasis as mentioned above. Keywords used were psoriasis, hand, feet, palm, sole, intertriginous, flexure, scalp, and nail.

In this era of evidence-based medicine, there is progressively increasing trend toward following scientifically logical treatment protocol as suggested by quality studies or from meta-analysis and systematic reviews. Evidence-based therapeutic guidelines assist the practicing physicians and dermatologists in delivering uniform, scientific, and evidence-based treatments to the patients. This article has been prepared after critically reviewing the published literature and the best evidence-based recommendations available.

What was known?

Evidence on therapies for the psoriasis of difficult-to-treat areas like palms and soles, nail, scalp, intertriginous areas is grossly lacking.

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reviewing these articles on psoriasis management and evaluating their level of evidence (LOE) as per the Oxford Centre for Evidence-Based Medicine 2011 guideline[1] [Table 1].

While dependency on evidence as obtained from meta-analysis and systematic review has increased exponentially, it is now also known that therapeutic recommendation, although should be based on, but not limited to the strict theoretical outcome obtained from these evidence-based analyses. Preparing any therapeutic suggestion requires consideration of various practical aspects and feasibility evaluation.

Socioeconomic, cultural, genetic, and ethnic factors play a significant role in therapeutic response of a drug. A major drawback while formulating any therapeutic guideline is lack of multiple well-designed trials conducted among population for which guideline is being planned.

Best care has been employed to prepare an appropriate and logical suggestion for the use of practicing physician to be used among Indian population and people of similar ethnic and socioeconomic background.

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Palmoplantar Psoriasis (Nonpustular)
Psoriasis of palms and soles is an important condition for various reasons. Diagnosis is not always straightforward considering frequent clinical overlap with chronic eczema. To complicate this, there is frequent co-localization of these two conditions. Incidence of development of psoriasis over persistent chronic eczema due to Koebner’s phenomena is not uncommon. Treatment of these two conditions will vary. Thus, proper diagnosis is essential for a successful outcome.

Palmoplantar areas may be affected in pustular psoriasis. This may be extensive involving many areas of the body or it may specifically located over the palms and soles. Palmoplantar pustular psoriasis, however, is not discussed here. Only classical plaque-type palmoplantar psoriasis (PPP) is described here.

PPP causes a significant psychological impact on the sufferer and hampers his/her daily activities. Management is difficult and more difficult than plaque psoriasis of nonpalmo-plantar areas.

Discussion on Evidence
There is serious lack of evidence. Continuous activities and trauma might adversely affect this. Thus, protection from trauma and frequent emollient application is generally advocated (LOE 5).

Topical treatment
Topical treatment is always preferred as the first-line therapy, but more than two-third of the patients require systemic therapy.

A randomized controlled trial (RCT) evaluated the comparative efficacy of topical 0.1% tazarotene cream and topical clobetasol propionate among 30 patients for 12 weeks. There was a good improvement in both without any significant difference between them. Complete clearance was noted among 52.9% and 61.5% of the patients, respectively, in tazarotene and clobetasol Group[1] (LOE 2).

Studies on other keratolytic agents such as salicylic acid are lacking. However, considering their safety and efficacy, many, including the author of this review, believe that these should be tried alone or in combination with other topicals such as topical corticosteroids (TCS) to reduce scaling (LOE 5).

Efficacy of calcipotriol has been reviewed.[2] One randomized study among 39 patients reported that twice weekly topical calcipotriol under occlusion was as effective twice daily application without occlusion[3] (LOE 2).

One retrospective analysis reported 12 out of 60 patients (20%) to have marked improvement with TCS while a similar extent of response was noticed among 17% (n = 5, total patients: 30) of patients who use only topical calcipotriol[4] (LOE 4).

Coal tar is another inexpensive agent and known to have some efficacy. Increased strength increases efficacy at the cost being increasingly cosmetically unacceptable. In a controlled trial, 6% crude coal tar was found to be better than salicylic acid and petroleum (both overnight, under occlusion). Coal tar resulted in good response among 76.5% of patients which was significantly higher than control group[5] (LOE 3).

| Table 1: The oxford 2011 levels of evidence |
|------------------------------------------|
| **Level 1**                             | **Level 2**                             | **Level 3**                              | **Level 4**                              | **Level 5** |
| Systematic review of randomized trials  | Randomized trial or observational study | Nonrandomized controlled cohort/follow-up study | Case series, case-control studies, or historically controlled studies | Mechanism-based reasoning |
| or n-of-1 trials                        | with dramatic effect                     |                                          |                                         |              |
One Cochrane review found one RCT that evaluated the comparative efficacy of narrowband ultraviolet B (NB-UVB) and topical psoralen-ultraviolet A (PUVA). There was no significant difference in terms of clearance rate.[4]

Topical PUVA was found to effectively improve in 63% of cases in an uncontrolled study on 48 patients[7] (LOE 3).

Topical PUVASol (alternate day) was compared with topical clobetasol propionate cream and coal tar daily. In both groups, patients perceived “good improvement.” Improvement or cure was noticed among 90% versus 75% of palmar lesions and 76% versus 79% of planar lesions, respectively, after TCS/tar and topical PUVASol therapies.[6]

Broadband UVB (BB UVB) and paint PUVA (pPUVA) have been compared among 248 patients (124 in each arm). pPUVA was found to have relatively higher efficacy. Complete remission was noticed among 36 (30%) and 53 (42%) and no response was found among 57 (47%) and 14 (11%) patients who were treated, respectively, with BB UVB and pPUVA.[8]

PUVA and NB-UVB have some efficacy. Studies are sparse, and psoralens have known adverse effect. Thus, NB-UVB is better in high resource setting, and PUVASol is better option as it is cheap and easily available everywhere. Topical PUVASol and pPUVA are advantageous as oral psoralens are not needed. Considering all the available literature, topical PUVASol or pPUVA appears preferable to PUVA and NB-UVB.

Studies have shown the efficacy of excimer laser (308 nm) in a case series[10] (LOE 4). However, this is expensive and not available widely.

**Systemic drugs**

A retrospective study evaluated the comparative efficacy of methotrexate (MTX) versus acitretin among 100 patients who had significant PPP. MTX was found to be significantly superior to acitretin after 12 weeks of therapy[11] (LOE 4). However, its extent of response is generally less than in psoriasis vulgaris and often requires higher dose.

In another study, MTX and acitretin were compared head to head. High-dose MTX (28 mg/week) appears to be significantly superior to 35 mg/day of acitretin[12] (LOE 2).

Only one retrospective study on cyclosporine (CyA) was found, in which only two patients were given CyA. There was a marked response in both (100%)[6] (LOE 4).

Results of a pooled analysis on apremilast from three large, multicenter, randomized, placebo-controlled studies reported a complete clearance of lesions in 46% of the treated group at 16th week[13] (LOE 1).

Infliximab (5 mg/kg, every 4 weeks) has been tried in a placebo-controlled randomized pilot trial among 24 patients. This pilot study did not reach its primary end point of M-PPASI 75 at week 14, but improvement was higher than placebo[14] (LOE 2).

One RCT and one open-label study had evaluated the efficacy of adalimumab in PPP. Efficacy was found in both the studies[15,16] (LOE 2).

Ustekinumab was found to be moderately effective in an open-label study[17] (LOE 3).

Unpublished data from one randomized, double-blind, placebo-controlled trial (GESTURE study) evaluated secukinumab among a large number of patients with PPP. One-third of the patients who were on secukinumab 300 mg had clear or almost clear palms and soles at week 16. The result was higher than secukinumab 150 mg and placebo. Overall, palmoplantar disease improved by more than 50% in patients on secukinumab 300 mg at week 16.

However, a pooled analysis of a previously published RCT[18] on secukinumab in plaque-type psoriasis revealed that its efficacy in PPP was efficacious in comparison to placebo[19] (LOE 2).

A single case report showed good response after combination therapy with etanercept and alitretinoin[20] (LOE 4). More studies are necessary.

**Suggested Therapeutic Protocol**

- Emollient is the first-line therapy and should be used as adjunctive to any other therapy. Topical keratolitics may be used as adjunctive therapy.
- Overall, this is resistant to treatments. Suggestion for a therapeutic ladder is difficult. In addition to efficacy, selection of drugs will depend on safety profile as frequently long-term treatment is necessary.
- Topical tazarotene, topical calcipotriol, and topical PUVASol/pPUVA have been compared with potent TCS and were found to have slightly less efficacy (mostly statistically insignificant difference). They all can be considered as the first-line therapy. They are safer than potent TCS and can be used for longer duration.
- Potent TCS may be preferred as the first-line therapy when faster response is required. However, safety data beyond 12 weeks are unknown and should be avoided.
- Topical tazarotene, topical calcipotriol, and topical PUVASol/pPUVA can also be considered as the first-line therapy. They are safer than potent TCS and can be used for longer duration and also be used after TCS as maintenance therapy.
- Topical calcipotriol can be used under occlusion intermittently for faster response and higher efficacy and for avoiding daily therapy.
- Topical coal tar is another option possibly of lesser efficacy than the above-mentioned first-line topical
drugs. Higher available strength should be used. This can be considered as the second-line topical drug and may be tried before systemic drugs are used.

- Phototherapy in the form of 308-nm UVB monochromatic excimer light is effective, possibly safe, but expensive. This can be used if facility is available.
- MTX is the systemic drug of choice and is used when topical and phototherapies fail. However, higher dose is necessary.
- Acitretin is less effective than MTX. This can be tried in cases that do not respond to MTX.
- Apremilast and many biologics (many tumor necrosis factor inhibitors [TNFi] other than infliximab), secukinumab, and ustekinumab have shown variable efficacy. They can be used when standard therapies have failed.

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Nail Psoriasis

Isolated nail psoriasis often has a significant impact on the quality of life. Apart from its impact of psychosocial aspect, nail psoriasis is often painful. Thus, despite very limited disease, it sometimes requires aggressive management.

Overall, nail psoriasis is a difficult condition to treat. Complete resolution of nail lesions is hard to achieve.

Selection of the best systemic treatment modality should be judged on overall disease burden, not only nail lesions when nail psoriasis is associated with significant involvement of other areas such as skin and joint. Drugs selected for treatment should ideally have beneficial effect on all areas avoiding the use of multiple drugs.

Discussion on Evidence

Topical therapy

In a randomized, double-blind, vehicle-controlled trial involving 31 patients with fingernail psoriasis, 0.1% tazarotene gel resulted in significant improvement in pitting and onycholysis after 24 weeks(1) (LOE 2).
Two other prospective studies showed improvement in hyperkeratosis, oil-spot discoloration, onycholysis, and pitting after 12 weeks[6,7] (LOE 3).

A prospective study done among 20 patients with short-contact dithranol therapy reported improvement after 5 months among 60% of patients, particularly in onycholysis, subungal hyperkeratosis, and to a lesser extent pitting[4] (LOE 3).

Studies have reported the efficacy of clobetasol nail lacquer. Ten patients with both nail-bed and matrix psoriasis were treated with 8% clobetasol-17-propionate nail lacquer in a prospective study. It was applied once daily for 21 days and then twice weekly for 9 months. Improvement was noticed within 4 weeks. There was no local or systemic secondary effects[5] (LOE 3).

Different strengths of clobetasol (0.05%, 1%, and 8%) in the lacquer were compared in a RCT and 8% was found to be most effective[6] (LOE 2).

TCS has been evaluated along with topical calcipotriol. In a prospective study conducted among 62 patients, topical calcipotriol was given 5 days/week (week days) and topical clobetasol propionate on weekend days (2 times/week) for 6 months and followed up for another 6 months. Treatment response was evaluated only as per patients’ response. Good response was noted among 43.7% and 41.5% of patients with finger and toe nail involvement, respectively, and excellent improvement was noted among 33.3% and 26.4% of patients, respectively. No side effects of TCS was found[7] (LOE 3).

However, comparative studies found overall limited efficacy of TCS. Combination of topical betamethasone dipropionate with salicylic acid was not superior to topical calcipotriol ointment monotherapy as found in a RCT. Both reported 50% reduction in fingernail subungal hyperkeratosis after 5 months[8] (LOE 2).

Addition of topical betamethasone dipropionate to topical calcipotriol also did not add any significant benefit as reported in another RCT. However, calcipotriol was used twice daily and the combination was used once daily leading to difficulty in evaluation[9] (LOE 2).

**Intralesional injection**

Despite extreme paucity of data, injection of triamcinolone acetonide (generally in the dose of 0.1 to 0.2 mL of 5- to 10-mg/mL suspension) into the lateral nail folds is considered reasonably satisfactorily effective. This is painful and this can be managed with nerve block or other methods[10,11] (LOE 3).

This method is best suited for nail psoriasis not associated with psoriasis involving other areas[12] (LOE 5).

Dermojet may be an alternative to injection but is costly and there is lack of evidence (LOE 5).

**Systemic therapy**

One open-label study with low-dose acitretin 0.2–0.3 mg/kg/day resulted in 41% mean reduction in their NAPSI score after 6 months among 36 patients with moderate-to-severe isolated nail psoriasis[13] (LOE 3).

MTX (15 mg/week) and CyA (5 mg/kg/week) resulted in equal and significant improvement in NAPSI score as found in a RCT done among 34 patients for 24 weeks[14] (LOE 2).

Many RCTs and multicentric studies and even systematic reviews are now available proving the efficacy of TNFi and other biologics such as ustekinumab, briakinumab, and alefacept.[15-31]

Infliximab offers a fast response. Improvement is found in one RCT[16] (LOE 2). One study reported 78%–80% improvement in NAPSI and improvement in quality of life[19,20] (LOE 3 and 4).

Many studies (RCTs, open-label, and retrospective studies) are available showing statistically significant efficacy of adalimumab[21-23] (LOE 2 and 4), etanercept[24-26] (LOE 4), and ustekinumab[27-29] (LOE 3).

Studies have reported newer drugs such as certolizumab pegol[30] (LOE 2) and golimumab[31] to be effective. More studies are required (LOE 2).

Apremilast showed 50% reduction from baseline in target nail in a recently published RCT. Improvements were generally maintained over 52 weeks[32] (LOE 2).

**Suggested Therapeutic Protocol**

- When treatment is required only for nail disease, topical therapies are started first, failing which systemic therapies may be started depending on the severity, symptoms, psychosocial impact, and patient’s willingness to take systemic therapy
- When disease involves skin and/or joints, treatment should be directed toward overall management of the disease. Thus, in such cases, drugs that have overall efficacy should be chosen
- Topical anthralin, calcipotriol, and tazarotene are safe and considered the first-line topical therapies
- TCS (nail lacquer preferred if available) can be used for shorter period when other topicals fail. Side effects may be avoided with infrequent use along with combining this with other topicals such as calcipotriol or tazarotene
- Intralesional triamcinolone (10 mg/ml) may be tried only in isolated nail disease when other topicals have failed and ideally in patients not having psoriasis of skin
- MTX and acitretin may be used as the first-line systemic drugs
- Cyclosporin may also be used as the second-line systemic drug
- Many biologics are effective. However, no comparative efficacy with conventional systemic
drugs is known. They may be used as third-line systemic drugs. Choice of individual biological may depend on the cost and type of associated psoriasis.

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Scalp Psoriasis

Treating scalp psoriasis is difficult because of poor accessibility and less convenience. Response to medication is poor. Disease aggravation from itching and other forms of trauma is another problem.

Discussion on Evidence

Topical therapy

Calcipotriol solution was found to be better than placebo in many well-designed trials (LOE 2).

TCS are known to effective in the form of lotion, foam, or shampoo. Clobetasol propionate shampoo, betamethasone valerate solution as well as betamethasone valerate foam were found to be better than calcipotriol solution (LOE 2).

In two different RCTs, clobetasol propionate foam was found to be better than placebo and clobetasol propionate solution of same strength at 2 weeks (LOE 2).

In a RCT, clobetasol propionate shampoo was found to be significantly better than vehicle at 4 weeks (LOE 2).

In another RCT, maintenance of clobetasol shampoo twice weekly was also found to be better than vehicle (LOE 2).

In another RCT, clobetasol propionate shampoo (0.05%) was also reported to be better than calcipotriol solution (LOE 2).

Betamethasone dipropionate was found to be better than clobetasol propionate solution in one study and inferior in another study (LOE 2).

Safety of TCS beyond 4 weeks is unknown. Also unknown is the most ideal TCS with the best strength and safety profile and the most ideal vehicle.

It has been reported in the recently published Cochrane review that combination of TCS and calcipotriene is the best topical drug considering the efficacy and safety. However, it has also been mentioned that the efficacy of such combination is marginally higher than isolated TCS. Thus, when used for short term, there is no advantage of adding topical calcipotriol and only CS may be chosen (LOE 1).

Calcipotriol, known to be less effective than TCS, may be used for short term, there is no advantage of adding topical calcipotriol and only CS may be chosen (LOE 1). This improvement persisted for 32 weeks (LOE 2).

In one RCT done with adalimumab, authors reported that patients with scalp psoriasis exhibited a median decrease of 100%. Severe adverse events were reported in 5.5% of patients (LOE 2).

Good-quality studies have reported a significant efficacy of etanercept (LOE 2), infliximab (LOE 2), ixekizumab (LOE 2), and secukinumab (ongoing trial).

Case reports have been published on ustekinumab proving its efficacy (LOE 4).
Suggested Therapeutic Protocol

- In mild-to-moderate disease, TCS are the first-line drugs. They are more potent than topical calcipotriol and tar. This should be used for shorter period (<4 weeks). Clobetasol propionate and betamethasone dipropionate are most effective. However, milder potent CS may also be used depending on the severity. Intermittent use or use of shampoos as maintenance therapy may avoid side effects
- Topical calcipotriene as a sole therapy is less efficacious but offers safety over the prolonged use of TCS. For short course, isolated TCS is preferred and for long-term therapy, topical calcipotriene is preferred
- When topical calcipotriene is found less efficacious, this may be combined with intermittent TCS
- Topical salicylic acids may be added to remove scale
- Coal tar (in the most favorable formulation available) and topical dithranol may be tried as they are cheap and known to be effective to some extent
- More severe disease may require addition of systemic drugs. Traditional systemic drugs such as acitretin, MTX, and CyA may be used. Presence, extent, and type of psoriasis in the other body areas may dictate the drug to be chosen
- Biologics may be added when other drugs fail. Good data are available on the efficacy of apremilast, adalimumab, etanercept, infliximab, ixekizumab, and secukinumab.

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Intertriginous Psoriasis

Intertriginous psoriasis (IP) is frequently misdiagnosed with intertrigo. Treatment is difficult because of the highly sensitive location that precludes the use of TCS and many other topical drugs. Safety is of prime importance in treating IP.

Discussion on Evidence

A single-center, double-blind, RCT compared the efficacy and safety of 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone valerate in the treatment of IP for 4 weeks and found the highest efficacy of 0.1% betamethasone valerate and the least efficacy of 1% pimecrolimus. No adverse effect of TCS was detected. Efficacy of calcipotriol was less than TCS but the difference was insignificant[1] (LOE 2).

Topical calcipotriol sometimes causes irritation. Calcitriol has been found to be superior and less irritating than calcipotriol[2] (LOE 2).

Although long-term safety or efficacy was not studied in any study, the result from the above study can be utilized to recommend topical calcipotriol as the preferred treatment for long-term treatment of IP. Topical calcineurin inhibitors such as 1% pimecrolimus can be used when calcipotriol cannot be used (LOE 5).

Many good-quality studies have proven the efficacy of topical tacrolimus in IP[3-4] (LOE 2).

There has been extreme scarcity of studies on systemic drugs in IP, both conventional systemic and biologics should work in this condition.

A single case report showed significant benefit from three injections of ustekinumab[7] (LOE 5).

Suggested Therapeutic Protocol

- Topical Vitamin D3 (calcitriol preferred over calcipotriol) is the first-line therapy. It is also preferred for long-term maintenance therapy
- Topical mild CSs may be used for short period when topical Vitamin D3 fails
- Calcineurin analogs (tacrolimus ointment or pimecrolimus cream) can also be used for long-term maintenance therapy
- Systemic drugs (conventional or biological) in case of resistant or severe disease.

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Conclusion

Evidence-based medicine is the most accurate method of collating the available scientific data. However, there are some weaknesses too. Outcome of even systematic review may not find the universal truth. Result of very high-quality evidences such as meta-analysis has been contradicted by subsequently done large RCT. Some bias may still exist.

Nevertheless, the great scientific credibility of evidence-based medicine being stated and accepted, there is no scope for ignoring one vital issue in planning a therapeutic recommendation based on the scientific evidence. Result obtained from RCTs and even systematic reviews may not appear feasible in the practical field. As mentioned earlier, many social, religious, economical, and regional factors become crucial while proposing any therapeutic recommendation to be successfully used in the field.

This review is an updated evidence-based review of the available articles on the management of “psoriasis...
of difficult-to-treat areas” and a proposed therapeutic recommendation based on the evidence. Many practical issues were considered while the therapeutic recommendation is proposed. It is expected that this will be helpful for the practicing physicians of India and many other countries having similar patient profile in terms of socioeconomic, cultural, racial, and genetic parameters.

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Conflicts of interest
There are no conflicts of interest.

What is new?
This document provides updated evidence on the management of psoriasis of difficult-to-treat areas and suggests practical, scientific and logical treatment options for these conditions.