

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

Nilendu Sarma

Abstract

Psoriasis is resistant to treatment and it shows frequent relapse; systemic treatment is often associated with toxicities, and long-term safety data are lacking for most of the newer drugs like biologics. Moreover, some body areas such as hands, feet, intertriginous areas, scalp, and nails are even more resistant. Frequently, systemic treatments are necessary considering the higher psychological impact on the patient. There is a lack of agreement on the best therapeutic modalities in the management of psoriasis involving difficult-to-treat locations. At present, there are no Indian guidelines for these conditions. Available literature has been reviewed extensively on the treatment of psoriasis involving difficult-to-treat locations; level of evidence has been evaluated as per the Oxford Centre for Evidence-Based Medicine 2011 guideline, and therapeutic suggestions have been developed. Best care has been employed to consider socioeconomic, cultural, genetic, and ethnic factors to prepare a therapeutic suggestion that is appropriate and logical to be used among Indian population and people of similar ethnic and socioeconomic background.

Key Words: Acral, difficult-to-treat area, flexure, intertriginous, nail, palm, psoriasis, scalp, sole

From the Department of Dermatology, Dr B. C. Roy Post Graduate Institute of Pediatric Sciences, Kolkata, West Bengal, India

Address for correspondence:

Dr. Nilendu Sarma,
P. N. Colony, Sapui Para, Bally,
Howrah - 711 227, West Bengal,
India.
E-mail: nilendusarma@yahoo.co.in

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

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 trouble 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

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Sarma N. Evidence and suggested therapeutic approach in psoriasis of difficult-to-treat areas: Palmoplantar psoriasis, nail psoriasis, scalp psoriasis, and intertriginous psoriasis. *Indian J Dermatol* 2017;62:113-22.

Received: September, 2016. **Accepted:** February, 2017.

Access this article online

<p>Quick Response Code:</p> 	<p>Website: www.e-ijd.org</p>
	<p>DOI: 10.4103/ijd.IJD_539_16</p>

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.

References

1. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. Available from: <http://www.cebm.net/index.aspx?o=5653>. [Last accessed 2015 Nov 08].

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 or n-of-1 trials	Randomized trial or observational study with dramatic effect	Nonrandomized controlled cohort/follow-up study	Case series, case-control studies, or historically controlled studies	Mechanism-based reasoning

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.^[6]

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 plantar lesions, respectively, after TCS/tar and topical PUVAsol therapies.^[8]

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.^[9]

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%)^[4] (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 keratolytics 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 fail.

References

1. Mehta BH, Amladi ST. Evaluation of topical 0.1% tazarotene cream in the treatment of palmoplantar psoriasis: An observer-blinded randomized controlled study. *Indian J Dermatol* 2011;56:40-3.
2. Thiers BH. The use of topical calcipotriene/calcipotriol in conditions other than plaque-type psoriasis. *J Am Acad Dermatol* 1997;37(3 Pt 2):S69-71.
3. Duweb GA, Abuzariba O, Rahim M, al-Taweel M, al-Alem S, Abdulla SA. Occlusive versus nonocclusive calcipotriol ointment treatment for palmoplantar psoriasis. *Int J Tissue React* 2001;23:59-62.
4. Adisen E, Tekin O, Gülekon A, Gürer MA. A retrospective analysis of treatment responses of palmoplantar psoriasis in 114 patients. *J Eur Acad Dermatol Venereol* 2009;23:814-9.
5. Kumar B, Kumar R, Kaur I. Coal tar therapy in palmoplantar psoriasis: Old wine in an old bottle? *Int J Dermatol* 1997;36:309-12.
6. Chen X, Yang M, Cheng Y, Liu GJ, Zhang M. Narrow-band ultraviolet B phototherapy versus broad-band ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis. *Cochrane Database Syst Rev* 2013, Issue 10. Art. No.: CD009481. DOI: 10.1002/14651858.CD009481.pub2.
7. Carrascosa JM, Plana A, Ferrándiz C. Effectiveness and safety of psoralen-UVA (PUVA) topical therapy in palmoplantar psoriasis: A report on 48 patients. *Actas Dermosifiliogr* 2013;104:418-25.
8. Khandpur S, Sharma VK. Comparison of clobetasol propionate cream plus coal tar vs. topical psoralen and solar ultraviolet A therapy in palmoplantar psoriasis. *Clin Exp Dermatol* 2011;36:613-6.
9. Lozinski A, Barzilai A, Pavlitsky F. Broad-band UVB versus paint PUVA for palmoplantar psoriasis treatment. *J Dermatolog Treat* 2016;27:221-3.
10. Goldberg DJ, Chwalek J, Hussain M. 308-nm Excimer laser treatment of palmoplantar psoriasis. *J Cosmet Laser Ther* 2011;13:47-9.
11. Spuls PI, Hadi S, Rivera L, Lebowitz M. Retrospective analysis of the treatment of psoriasis of the palms and soles. *J Dermatolog Treat* 2003;14 Suppl 2:21-5.
12. Janagond AB, Kanwar AJ, Handa S. Efficacy and safety of systemic methotrexate vs. acitretin in psoriasis patients with significant palmoplantar involvement: A prospective, randomized study. *J Eur Acad Dermatol Venereol* 2013;27:e384-9.
13. Bissonnette R, Pariser DM, Wasel NR, Goncalves J, Day RM, Chen R, *et al.* Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. *J Am Acad Dermatol* 2016;75:99-105.
14. Bissonnette R, Poulin Y, Guenther L, Lynde CW, Bolduc C, Nigen S. Treatment of palmoplantar psoriasis with infliximab: A randomized, double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol* 2011;25:1402-8.
15. Poulin Y, Crowley JJ, Langley RG, Unnebrink K, Goldblum OM, Valdecantos WC. Efficacy of adalimumab across subgroups of patients with moderate-to-severe chronic plaque psoriasis of the hands and/or feet: *Post hoc* analysis of REACH. *J Eur Acad Dermatol Venereol* 2014;28:882-90.
16. Richetta AG, Mattozzi C, Giancristoforo S, D'Epiro S, Cantisani C, Macaluso L, *et al.* Safety and efficacy of Adalimumab in the treatment of moderate to severe palmo-plantar psoriasis: An open label study. *Clin Ter* 2012;163:e61-6.
17. Au SC, Goldminz AM, Kim N, Dumont N, Michelon M, Volf E, *et al.* Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis. *J Dermatolog Treat* 2013;24:179-87.
18. Rich P, Sigurgeirsson B, Thaci D, Ortonne JP, Paul C, Schopf RE, *et al.* Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: A randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Br J Dermatol* 2013;168:402-11.
19. Paul C, Reich K, Gottlieb AB, Mrowietz U, Philipp S, Nakayama J, *et al.* Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: Subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. *J Eur Acad Dermatol Venereol* 2014;28:1670-5.
20. Meyer V, Goerge T, Luger TA, Beissert S. Successful treatment of palmoplantar hyperkeratotic psoriasis with a combination of etanercept and alitretinoin. *J Clin Aesthet Dermatol* 2011;4:45-6.

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^[2,3] (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, subungual 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 subungual 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.

References

- Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: A double-blind, randomized, vehicle-controlled study. *Cutis* 2001;68:355-8.
- Bianchi L, Soda R, Diluvio L, Chimenti S. Tazarotene 0.1% gel for psoriasis of the fingernails and toenails: An open, prospective study. *Br J Dermatol* 2003;149:207-9.
- Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: A double-blind study. *Acta Derm Venereol* 2007;87:167-8.
- Yamamoto T, Katayama I, Nishioka K. Topical anthralin therapy for refractory nail psoriasis. *J Dermatol* 1998;25:231-3.
- Sánchez Regaña M, Martín Ezquerro G, Umberto Millet P, Llambí Mateos F. Treatment of nail psoriasis with 8% clobetasol nail lacquer: Positive experience in 10 patients. *J Eur Acad Dermatol Venereol* 2005;19:573-7.
- Nakamura RC, Abreu LD, Duque-Estrada B, Tamler C, Leverone AP. Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: Prospective, controlled and randomized pilot study. *An Bras Dermatol* 2012;87:203-11.
- Rigopoulos D, Ioannides D, Prastitis N, Katsambas A. Nail psoriasis: A combined treatment using calcipotriol cream and clobetasol propionate cream. *Acta Derm Venereol* 2002;82:140.
- Tosti A, Piraccini BM, Cameli N, Kokely F, Plozzer C, Cannata GE, et al. Calcipotriol ointment in nail psoriasis: A controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol* 1998;139:655-9.
- Tzung TY, Chen CY, Yang CY, Lo PY, Chen YH. Calcipotriol used as monotherapy or combination therapy with betamethasone dipropionate in the treatment of nail psoriasis. *Acta Derm Venereol* 2008;88:279-80.
- Bleeker JJ. Intralesional triamcinolone acetonide using the Port-O-Jet and needle injections in localized dermatoses. *Br J Dermatol* 1974;91:97-101.
- Nantel-Battista M, Richer V, Marciel I, Benohanian A. Treatment of nail psoriasis with intralesional triamcinolone acetonide using a needle-free jet injector: A prospective trial. *J Cutan Med Surg* 2014;18:38-42.
- Crowley JJ, Weinberg JM, Wu JJ, Robertson AD, Van Voorhees AS; National Psoriasis Foundation. Treatment of nail psoriasis: Best practice recommendations from the Medical Board of the National Psoriasis Foundation. *JAMA Dermatol* 2015;151:87-94.
- Tosti A, Ricotti C, Romanelli P, Cameli N, Piraccini BM. Evaluation of the efficacy of acitretin therapy for nail psoriasis. *Arch Dermatol* 2009;145:269-71.
- Gümüşel M, Özdemir M, Mevlitoglu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: A one-blind, randomized study. *J Eur Acad Dermatol Venereol* 2011;25:1080-4.
- Jemec GB, Ibler KS. Treatment of nail psoriasis with TNF- α or IL12/23 inhibitors. *J Drugs Dermatol* 2012;11:939-42.
- Saraceno R, Pietroleonardo L, Mazzotta A, Zangrilli A, Bianchi L, Chimenti S. TNF- α antagonists and nail psoriasis: An open, 24-week, prospective cohort study in adult patients with psoriasis. *Expert Opin Biol Ther* 2013;13:469-73.
- Kyriakou A, Patsatsi A, Sotiriadis D. Anti-TNF agents and nail psoriasis: A single-center, retrospective, comparative study. *J Dermatolog Treat* 2013;24:162-8.
- Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: A phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367-74.
- Reich K, Ortonne JP, Kerkmann U, Wang Y, Saurat JH, Papp K, et al. Skin and nail responses after 1 year of infliximab therapy in patients with moderate-to-severe psoriasis: A retrospective analysis of the EXPRESS Trial. *Dermatology* 2010;221:172-8.
- Rigopoulos D, Gregoriou S, Stratigos A, Larios G, Korfitis C, Papaioannou D, et al. Evaluation of the efficacy and safety of infliximab on psoriatic nails: An unblinded, nonrandomized, open-label study. *Br J Dermatol* 2008;159:453-6.
- Leonardi C, Langley RG, Papp K, Tying SK, Wasel N, Vender R, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: Efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. *Arch Dermatol* 2011;147:429-36.
- Sola-Ortigosa J, Sánchez-Regaña M, Umberto-Millet P. Efficacy of adalimumab in the treatment of psoriasis: A retrospective study of 15 patients in daily practice. *J Dermatolog Treat* 2012;23:203-7.
- Van den Bosch F, Manger B, Goupille P, McHugh N, Rødevand E, Holck P, et al. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. *Ann Rheum Dis* 2010;69:394-9.
- Luger TA, Barker J, Lambert J, Yang S, Robertson D, Foehl J, et al. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol* 2009;23:896-904.
- Coelho JD, Diamantino F, Lestre S, Ferreira AM. Treatment of severe nail psoriasis with etanercept. *Indian J Dermatol Venereol Leprol* 2011;77:72-4.
- Rallis E, Stavropoulou E, Rigopoulos D, Verros C. Rapid response of nail psoriasis to etanercept. *J Rheumatol* 2008;35:544-5.
- Patsatsi A, Kyriakou A, Sotiriadis D. Ustekinumab in nail psoriasis: An open-label, uncontrolled, nonrandomized study. *J Dermatolog Treat* 2013;24:96-100.
- Rigopoulos D, Gregoriou S, Makris M, Ioannides D. Efficacy of ustekinumab in nail psoriasis and improvement in nail-associated quality of life in a population treated with ustekinumab for cutaneous psoriasis: An open prospective unblinded study. *Dermatology* 2011;223:325-9.
- Byun SY, Kim BR, Choi JW, Youn SW. Severe nail fold psoriasis extending from nail psoriasis resolved with ustekinumab: Suggestion of a cytokine overflow theory in the nail unit. *Ann Dermatol* 2016;28:94-7.
- Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014;73:48-55.
- Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60:976-86.

32. Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, *et al.* Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *J Am Acad Dermatol* 2016;74:134-42.

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^[1] (LOE 2).

TCS are known to be effective in the form of lotion, foam, or shampoo. Clobetasol propionate shampoo, betamethasone valerate solution^[2] as well as betamethasone valerate foam^[3] were found to be better than calcipotriol solution (LOE 2).

In two different RCTs, clobetasol propionate foam was found to be better than placebo^[4] and clobetasol propionate solution^[4,5] 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^[6] (LOE 2).

In another RCT, maintenance of clobetasol shampoo twice weekly was also found to be better than vehicle^[7] (LOE 2).

In another RCT, clobetasol propionate shampoo (0.05%) was also reported to be better than calcipotriol solution^[8] (LOE 2).

Betamethasone dipropionate was found to be better^[9] than clobetasol propionate solution in one study and inferior in another study^[10] (LOE 2).

Safety of TCS beyond 4 weeks is unknown.^[11] 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^[12] (LOE 1). Calcipotriol, known to be less effective than TCS, may be used for maintenance therapy beyond 4 weeks.

Coal tar has been used in scalp psoriasis for many years because it is cheap, available, and possibly effective. There is extreme paucity of evidence on coal tar in scalp psoriasis. In an uncontrolled prospective

study among patients with scalp psoriasis, coal tar gel was used only for 5 days and reported to be effective^[13] (LOE 3).

Coal tar is, however, cosmetically less acceptable and may stain clothes. There is a concern for its possible risk of carcinogenicity as found in some animal studies. However, evidence is lacking to prove or disprove this risk in humans when it is used in psoriasis.^[14] The American Academy of Dermatology mentions "low risk" for its use in pregnant women when used for short period and has advocated to use "with caution" in children. German guideline has, however, mentioned pregnancy and nursing as absolute contraindications.

In a recently published retrospective, population-based, case-control study that was done among 1387 cases diagnosed with bladder cancer and 5182 population controls, no evidence of increased bladder cancer risk from coal tar was detected. Another huge previously done cohort study, conducted among 13,200 patients with psoriasis and eczema, also did not find any increased cancer risk from this drug^[15] (LOE 4).

Topical keratolytics such as salicylic acids are known to be helpful as an adjunctive therapy along with TCS when there is thick scaling.

Anthralin is another age-old drug known to be effective. Despite paucity of data, this may be used (LOE 5).

Phototherapy is difficult in scalp. Fiber-optic UVB comb 3 times weekly for 12 weeks was reported to be effective^[16] (LOE 3). A 308-nm excimer laser, a UV light source, was also reported to be effective^[17] (LOE 3).

Systemic therapy

RCTs on the use of traditional systemic drugs were absolutely sparse. However, it is well known that these drugs when used for other body areas also improve the scalp lesions.

Apremilast has been reported to be highly effective in at least three studies. In a phase III RCT (ESTEEM 1 and ESTEEM 2), apremilast, an oral phosphodiesterase 4 inhibitor, when used at a dose of 30 mg twice daily for 16 weeks, showed significantly higher improvement in scalp psoriasis in comparison to placebo. This improvement persisted for 32 weeks^[18] (LOE 2).

In one RCT done with adalimumab, authors reported that patients with scalp psoriasis exhibited a median decrease from baseline Psoriasis Scalp Severity Index at week 16 of 100%. Severe adverse events were reported in 5.5% of patients^[19] (LOE 2).

Good-quality studies have reported a significant efficacy of etanercept^[20,21] (LOE 2), infliximab^[22] (LOE 2), ixekizumab^[23] (LOE 2), and secukinumab (ongoing trial).^[24]

Case reports have been published on ustekinumab proving its efficacy^[25,26] (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 shampoo 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.

References

1. Green C, Ganpule M, Harris D, Kavanagh G, Kennedy C, Mallett R, *et al.* Comparative effects of calcipotriol (MC903) solution and placebo (vehicle of MC903) in the treatment of psoriasis of the scalp. *Br J Dermatol* 1994;130:483-7.
2. Thaçi D, Daiber W, Boehncke WH, Kaufmann R. Calcipotriol solution for the treatment of scalp psoriasis: Evaluation of efficacy, safety and acceptance in 3,396 patients. *Dermatology* 2001;203:153-6.
3. Klaber MR, Hutchinson PE, Pedvis-Leftick A, Kragballe K, Reunala TL, Van de Kerkhof PC, *et al.* Comparative effects of calcipotriol solution (50 micrograms/ml) and betamethasone 17-valerate solution (1 mg/ml) in the treatment of scalp psoriasis. *Br J Dermatol* 1994;131:678-83.
4. Andreassi L, Giannetti A, Milani M; Scale Investigators Group. Efficacy of betamethasone valerate mousse in comparison with standard therapies on scalp psoriasis: An open, multicentre, randomized, controlled, cross-over study on 241 patients. *Br J Dermatol* 2003;148:134-8.
5. Gottlieb AB, Ford RO, Spellman MC. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of non-scalp regions. *J Cutan Med Surg* 2003;7:185-92.
6. Bergstrom KG, Arambula K, Kimball AB. Medication formulation affects quality of life: A randomized single-blind study of clobetasol propionate foam 0.05% compared with a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. *Cutis* 2003;72:407-11.
7. Jarratt M, Breneman D, Gottlieb AB, Poulin Y, Liu Y, Foley V. Clobetasol propionate shampoo 0.05%: A new option to treat patients with moderate to severe scalp psoriasis. *J Drugs Dermatol* 2004;3:367-73.
8. Reygagne P, Mrowietz U, Decroix J, de Waard-van der Spek FB, Acebes LO, Figueiredo A, *et al.* Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: A randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatolog Treat* 2005;16:31-6.
9. Katz HI, Lindholm JS, Weiss JS, Shavin JS, Morman M, Bressinck R, *et al.* Efficacy and safety of twice-daily augmented betamethasone dipropionate lotion versus clobetasol propionate solution in patients with moderate-to-severe scalp psoriasis. *Clin Ther* 1995;17:390-401.
10. Lassus A. Local treatment of psoriasis of the scalp with clobetasol propionate and betamethasone-17,21-dipropionate: A double-blind comparison. *Curr Med Res Opin* 1976;4:365-7.
11. van der Vleuten CJ, van de Kerkhof PC. Management of scalp psoriasis: Guidelines for corticosteroid use in combination treatment. *Drugs* 2001;61:1593-8.
12. Schlager JG, Rosumeck S, Werner RN, Jacobs A, Schmitt J, Schlangere C, *et al.* Topical treatments for scalp psoriasis. *Cochrane Database Syst Rev* 2016;2:CD009687.
13. Langner A, Wolska H, Hebborn P. Treatment of psoriasis of the scalp with coal tar gel and shampoo preparations. *Cutis* 1983;32:290-1, 295-6.
14. Roelofzen JH, Aben KK, Van de Kerkhof PC, Van der Valk PG, Kiemeneij LA. Dermatological exposure to coal tar and bladder cancer risk: A case-control study. *Urol Oncol* 2015;33:20.e19-22.
15. Roelofzen JH, Aben KK, Oldenhof UT, Coenraads PJ, Alkemade HA, van de Kerkhof PC, *et al.* No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *J Invest Dermatol* 2010;130:953-61.
16. Taneja A, Racette A, Gourgouliatos Z, Taylor CR. Broad-band UVB fiber-optic comb for the treatment of scalp psoriasis: A pilot study. *Int J Dermatol* 2004;43:462-7.
17. Taylor CR, Racette AL. A 308-nm excimer laser for the treatment of scalp psoriasis. *Lasers Surg Med* 2004;34:136-40.
18. Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, *et al.* Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *J Am Acad Dermatol* 2016;74:134-42.
19. Thaçi D, Unnebrink K, Sundaram M, Sood S, Yamaguchi Y. Adalimumab for the treatment of moderate to severe psoriasis: Subanalysis of effects on scalp and nails in the BELIEVE study. *J Eur Acad Dermatol Venereol* 2015;29:353-60.
20. Moore A, Gordon KB, Kang S, Gottlieb A, Freundlich B, Xia HA, *et al.* A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *J Am Acad Dermatol* 2007;56:598-603.
21. Bagel J, Lynde C, Tying S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: A randomized, double-blind, placebo-controlled study of etanercept. *J Am Acad Dermatol* 2012;67:86-92.
22. Kalb RE, Blauvelt A, Sofen HL, Chevrier M, Amato D, Calabro S, *et al.* Effect of infliximab on health-related quality of life and disease activity by body region in patients with moderate-to-severe psoriasis and inadequate response to etanercept: Results from the PSUNRISE trial. *J Drugs Dermatol* 2013;12:874-80.
23. Langley RG, Rich P, Menter A, Krueger G, Goldblum O,

- Dutronic Y, *et al.* Improvement of scalp and nail lesions with ixekizumab in a phase 2 trial in patients with chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 2015;29:1763-70.
24. Lebwohl M, Qureshi A, Kianifard F. Secukinumab in the treatment of moderate to severe scalp psoriasis: A study to evaluate efficacy and safety. *J Am Acad Dermatol* 2015;72 5 Suppl 1:AB250.
 25. Di Cesare A, Fargnoli MC, Peris K. Rapid response of scalp psoriasis to ustekinumab. *Eur J Dermatol* 2011;21:993-4.
 26. Papadavid E, Ferra D, Koumaki D, Dalamaga M, Stamou C, Theodoropoulos K, *et al.* Ustekinumab induces fast response and maintenance of very severe refractory scalp psoriasis: Results in two Greek patients from the psoriasis hospital-based clinic. *Dermatology* 2014;228:107-11.

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^[3-6] (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.

References

1. Kreuter A, Sommer A, Hyun J, Bräutigam M, Brockmeyer NH, Altmeyer P, *et al.* 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: A double-blind, randomized controlled study. *Arch Dermatol* 2006;142:1138-43.
2. Ortonne JP, Humbert P, Nicolas JF, Tsankov N, Tonev SD, Janin A, *et al.* Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg g(-1) ointment and calcipotriol 50 microg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol* 2003;148:326-33.
3. Lebwohl M, Freeman AK, Chapman MS, Feldman SR, Hartle JE, Henning A; Tacrolimus Ointment Study Group. Tacrolimus ointment is effective for facial and intertriginous psoriasis. *J Am Acad Dermatol* 2004;51:723-30.
4. Gribetz C, Ling M, Lebwohl M, Pariser D, Draelos Z, Gottlieb AB, *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: A double-blind, randomized study. *J Am Acad Dermatol* 2004;51:731-8.
5. Freeman AK, Linowski GJ, Brady C, Lind L, Vanveldhuisen P, Singer G, *et al.* Tacrolimus ointment for the treatment of psoriasis on the face and intertriginous areas. *J Am Acad Dermatol* 2003;48:564-8.
6. Martín Ezquerro G, Sánchez Regaña M, Herrera Acosta E, Umberto Millet P. Topical tacrolimus for the treatment of psoriasis on the face, genitalia, intertriginous areas and corporal plaques. *J Drugs Dermatol* 2006;5:334-6.
7. Campos MA, Varela P, Baptista A, Moreira AI. Inverse psoriasis treated with ustekinumab. *BMJ Case Rep* 2016; pii: Bcr2016215019.

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.

Financial support and sponsorship

Nil.

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.