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Medication-Assisted Treatment of Nail Psoriasis

Amany Nassar[1], Rania Elakad[1],&Hadeel Atef Saeed[1]

[1]Department of Dermatology, Venereology and Andrology, Faculty of Medicine,Zagazig University, Alsharquia, Egypt.

ABSTRACT

Nail involvement occurs in 80–90% of patients with plaque psoriasis and is considerably more prevalent in psoriatic arthritis sufferers. This review is the result of a systematic review of the literature and includes information on topical, intralesional, conventional systemic, biologic systemic, and non-pharmacological treatments for nail psoriasis. According to existing research, all anti-tumor necrosis factor (TNF), anti-interleukin (IL)-17, and anti-IL-12/23 antibodies approved for plaque psoriasis and psoriatic arthritis are extremely effective treatments for nail psoriasis. Conventional systemic medications for nail psoriasis, such as methotrexate, cyclosporine, acitretin, and apremilast, as well as intralesional corticosteroids, may also be beneficial. Additionally, topical therapies such as corticosteroids, calcipotriol, tacrolimus, and tazarotene have been demonstrated to be effective in the treatment of nail psoriasis, particularly in mild cases. Finally, non-pharmacological treatment methods such as phototherapy, photodynamic therapy, laser therapy, and numerous radiotherapeutic possibilities are discussed but cannot be recommended as first-line therapy. Additionally, this analysis concludes that the absence of a credible core set of outcome measures for nail psoriasis trials impairs interpretation and is urgently required.

1. INTRODUCTION

Psoriasis is a widespread inflammatory skin disease that can be extremely stressful and cause severe morbidity. It is most frequently manifested as well-defined, scaling, and erythematous plaques, most frequently on the extensor surfaces of the knees and elbows. Prevalence ranges from 0.7 to 2.9 percent, with a preference for Caucasians. Plaque psoriasis (PP, or psoriasis vulgaris) is the most prevalent type of psoriasis, involving 85–90% of patients and manifesting as patches on the trunk and extremities. Other kinds of psoriasis are more frequent and may affect the scalp, joints, wrinkles, or nails, even in persons who do not have skin psoriasis.

Nail psoriasis is more than 50% prevalent in PP patients, with an estimated lifetime incidence of 80–90% **[1]**. According to a recent survey conducted by Klaassen et al., 66.0 percent of 1459 psoriasis patients had nail involvement, indicating that the frequency of nail psoriasis is frequently overestimated **[2]**. Nail psoriasis may be more than 80% prevalent in persons with psoriatic arthritis (PsA) **[3].** In the absence of cutaneous or joint illness, 5–10% of psoriatic patients have nail psoriasis **[4].** Psoriatic nail disease may be used to identify patients at risk of developing psoriatic joint injury in the coming future **[5].**

Nail psoriasis can appear clinically in a variety of ways depending on the structure implicated within the nail apparatus. All of the symptoms of nail psoriasis are non-specific and can occur in a variety of different nail disorders. Thus, histopathology of the affected tissue is the gold standard for diagnosing nail psoriasis; nonetheless, in the majority of cases, clinical pattern identification can be used to diagnose nail psoriasis. When psoriasis affects the nail matrix (the nail plate), the following symptoms may occur: pitting, leukonychia (white spots within the nail plate), red spots on the lunula, transverse grooves (Beau's lines), and crumbling of the nail plate. Psoriasis of the nail bed manifests as oil-drop staining, distal third of the nail plate splinter hemorrhages, subungual hyperkeratosis, and/or nail plate separation from the nail bed (onycholysis). Psoriasis can also manifest as psoriatic paronychia in the periungual zone. When evaluating psoriatic nails, it is critical to consider the contribution of nail matrix and nail bed disease individually, as some treatment approaches are more effective at treating matrix illness than others are at treating nail bed disease.

It is known that psoriasis on visible areas of the skin, such as the face and hands, may have a substantial negative impact on physical, psychological, and social dimensions of quality of life (QoL) **[6]**. In addition, fingernail psoriasis is highly visible and has a relevant and additional negative impact on the QoL of psoriasis patients, particularly in patients with both nail matrix and nail bed signs of the disease **[7].** Patients with only nail bed alterations scored significant lower QoL scores when compared with patients with only nail matrix features. The additional negative consequences of nail involvement

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in psoriasis on QoL may be explained by the fact that nail psoriasis is more than a highly visible variant. Complaints of patients with nail psoriasis include pain, inability to grasp small objects, tie shoelaces or button clothes, and cause an altered sense of fine touch. Pain in nail psoriasis has a high association with joint pain, therefore the presence of nail psoriasis may identify patients who are at risk of developing disabling PsA **[8].**

The impact of nail psoriasis on individual patients can be high. A recent survey showed that 47 % of patients with nail psoriasis would like to receive treatment for their nail disorder **[2]**; however, treatment of nail psoriasis is challenging, and involves topical, intralesional, and systemic therapies. A recent Cochrane review discussed randomized controlled trials (RCTs) on nail psoriasis **[9].** The practical use of that review is limited by the fact that most studies on nail psoriasis are largely anecdotal, case-series, or derived from open-label, prospective studies. Therefore, several frequently used, and considered effective, treatment options are not discussed in that Cochrane review. The aim of that review was to cover all published data on the treatment of nail psoriasis, including not only data from RCTs but also from other studies and case reports.

2. PATHOPHYSIOLOGY

While the etiology of psoriasis is not fully understood, studies support the hypothesis that psoriasis develops as a result of the interaction of an individual's genetic susceptibility (up to 70% concordance in monozygotic twins), specific environmental factors and the immune system **[10].**

2.1. Genetic factors

There is a known genetic component of psoriasis pathogenesis. Those with a first-degree relative with psoriasis have an approximately 5-fold increased risk of developing the disease as compared with the general population and many children with psoriasis have a first-degree relative with the disease. Furthermore, monozygotic twins have a higher concordance rate than dizygotic twins of developing psoriasis **[11].**

Approximately 70% of individuals with pediatric psoriasis have a positive family history for the condition. Psoriasis develops in 8% of siblings of persons with the disease when neither parent is affected, in 16% when one parent is affected and in 50% of siblings when both parents have the disease **[12].**

Several chromosomal regions, termed psoriasis susceptibility loci (PSORS), have been linked to a risk of developing psoriasis. There is a strong association of the HLA-Cw6 allele with early-onset disease. Among different PSORS the strongest association is with the major histocompatibility complex (MHC) on chromosome 6p21 (PSORS1) which accounts for around 50% of the heritability of the disease **[13].**

The role of genetic factors in psoriasis has been confirmed from family and twin studies. Several other gene regions, including those encoding some of the implicated interleukins as IL-23 signaling (IL23A, IL23R, IL12B), modulation of Th2 immune responses (IL4, IL13) and activated B cell (NF-κB) signaling tumor necrosis factor α–induced protein 3-interacting protein 1 (TNFAIP3 interacting protein 1(TNIP1) have been identified in some affected populations **[14].**

Meanwhile, around 40 additional loci have been found to be associated with psoriasis. Many of the potentially corresponding genes point toward a central role of both the innate as well as the adaptive immune system. However, this immunopathogenetic model only applies to the skin, as recent studies failed to demonstrate a HLA-Cw6 association with the nails or joints. Furthermore, the nails and joints are intimately associated with inflammation at points of ligament or tendon insertion (i.e., enthesitis) **[15].**

Moreover, inflammation at insertion sites and nails does not appear to be associated with a particular antigenic territory but is quite diffuse in nature. This suggests that an aberrant response to tissue stressing of the integrated nail-joint apparatus, rather than autoimmunity, is driving the inflammatory process. Therefore, HLA-Cw6-associated skin psoriasis is more closely linked to autoimmunity, whereas nail and joint disease may be linked to tissue-specific factors, including tissue biomechanical stressing and microtrauma, that lead to activation of aberrant innate immune responses **[16].**

However, a case of skin and NP definitely disappearing after allogeneic bone marrow transplantation is more in favor of predominant immunogenetic factors **[17].**

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2.2. Environmental factors

Factors known to induce or worsen psoriasis include mild localized trauma, such as scratching, piercings, tattoos, sunburns, chemical irritants ("classical" Koebner phenomenon) and drugs, including β-blockers, lithium, antimalarials, and non-steroidal anti-inflammatory drugs **[18].**

Certain infections, especially Candida albicans have been shown to play a role in the exacerbation and maintenance of NP by activation of antimicrobial peptide cathelidin (LL37) and Th17. Candida can stimulate the production of superantigens, determining nonspecific T-cell activation and secretion of cytokines that can initiate the psoriatic process **[19].**

The climate in general and exposure to natural sun light in particular are discussed as additional extrinsic factors that have an important impact on disease activity. Some researchers suggest the ultraviolet index is of interest based on the known effects of weather patterns on cutaneous psoriasis and PsA, which both worsen during winter and improve during summer **[20].**

3. MANAGEMENT OF NAIL PSORIASIS

Treating nail psoriasis is often a time-consuming challenge with an unsecure outcome. Response to treatment may appear everywhere in the spectrum, from very disappointing to excellent, but relapses are common. Unfortunately, there is a lack of evidence-based treatments and consequent guidelines. This does not necessarily mean that available treatments are not efficacious, but that final statistical evidence is missing. Therapeutic options include patient education, external topical treatments, intralesional steroids, systemic treatments, and non-pharmacological treatment options. Patient education should cover the avoidance of minor repetitive nail trauma, managing expectations with regard to the amount of time necessary for nail clearing, and discussing prevention and treatment of fungal infections in psoriasis nails.

The choice of treatments depends on clinical presentation, as well as patient-related factors. Most patients have only mild nail psoriasis without signs of PsA or severe PP. These patients may profit from topical treatment, while systemic treatment is indicated in patients with severe nail psoriasis, major impact on QoL, or concomitant moderate to severe psoriatic skin lesions. Systemic therapy should also be favored if concomitant PsA is evident. The choice of treatments further depends on patient factors, including age, experienced burden of disease, accompanying diseases and therapies, individual patient preferences, and the risks of treatment.

This review covers treatment options for nail psoriasis and is the result of a systemic approach to the literature.

4.TREATMENT OF NAIL PSORIASIS

Although many effective therapies are available for psoriasis, unfortunately the same level of response is usually not seen for the nail involvement. Furthermore, validated quantitative assessment tools used to evaluate this response are still under constant review, and the resulting score might not reflect the true severity of the disease **[21].**

Effective treatment of NP is challenging on account of limited clinical evidence and guidelines for effective treatments and the lack of placebo-controlled, with adverse effects that limit patient adherence, clinical trials that have specifically assessed nail outcomes as the primary end point. To date, patients and physicians are often dissatisfied with current standard therapeutic approaches **[9].**

Current treatment modalities for NP can be classified into topical therapy, intralesional injections, photochemotherapy, laser therapy, radiotherapy, and systemic therapy including the use of biologic agents. In addition, education on general nail care measures should be emphasized as an integral part of the overall management. The treatment of NP largely depends on the severity of symptoms **[22].**

Local or topical therapies along with UV therapy should be attempted initially; however, the efficacy of these methods is limited owing to difficulty penetrating the nail or its matrix **[23].**

Systemic therapy is recommended when NP is associated with extensive cutaneous psoriatic lesions, if the lesions are severe or involve several nails (5 out of 10 or more), and if the disease has a significant impact on the patient's quality of life, interfering with the daily activities or if topical treatment fails. Systemic treatment is not recommended for patients with psoriasis limited to the nails. **[24].**

Patient satisfaction and compliance with current treatment modalities for NP are often low because of difficulties in administration, poor compliance, and inadequate long-term efficacy **[25].**

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4.1. General nail care

It is well known that the Koebner phenomenon occurs in psoriasis, whereby the formation of psoriatic lesions is triggered at sites of physical injury to the skin. Patient education should cover the avoidance of minor repetitive nail trauma such as nail biting, subungual cleaning, or manicure. Keeping the nails as short as possible is essential to prevent trauma or lifting of the poorly attached nail plate **[26].**

Before the start of treatment, the clinician should discuss with the patient that any noticeable nail improvement will take a long time. The low growth rate of the nail plate is responsible for a delay of 3–9 months before clinical improvement can be noticed. Four to 6 months is a reasonable period of treatment before evaluating results. Treatment of concomitant onychomycosis will improve the outcome of all other treatments **[2].**

4.2. Topical treatment

Creams, ointments and gels are the traditional topical formulations that have been formulated for the effective treatment of NP. However, these conventional topical formulations get promptly cleansed or wiped out and only a small fraction of active ingredient is able to diffuse through the nail. Nail lacquer can be considered a viable option that can offer increased residence and continuous controlled/ systemic release **[27].**

Medicated nail lacquers are relatively new dosage forms meant for transungual delivery of drug. It provides the advantage of long duration of contact between the nail and drug and therefore the effective concentration can be reached at desired site. When nail lacquer is applied it will form a water insoluble film on nail plate after the evaporation of volatile organic solvent. Film will contain the higher concentration of the drug **[28].**

For psoriasis affecting the nail matrix, treatment can be applied to the nail folds, but for nail bed psoriasis, onycholytic nails need to be trimmed back to the hyponychium before applying treatment as close as possible to the nail bed **[29]**.

The most commonly recommended treatments for NP involve the use of topical or intralesional corticoids, as well as the use of topical vitamin D3 analogues. Other topical treatments which have been shown to be effective include tacrolimus, fluorouracil, topical cyclosporine, tazarotene and anthralin **[30].**

4.3. Topical steroids

The clobetasol propionate at a concentration of 0.05% in cream or gel vehicle has been the most recommended topical treatment. However, they may cause atrophy, depigmentation, telangiectasia, and bone resorption. Consequently favorable results have been observed with 8% clobetasol 17- propionate lacquer that has effective transungual penetration and therapeutic effect both on nail bed and matrix lesions, while lacking side effects **[30].**

4.4. Vitamin D3

Vitamin D3 (calcitriol) and its analogs calcipotriol and tacalcitol are well established in the therapy of psoriasis vulgaris due to their effects on epidermal differentiation, proliferation, regulation of production and release of proinflammatory cytokines. Most studies were done with calcipotriol and tacalcitol. Apparently, their effect on nail bed lesions is more marked than on matrix signs **[17].**

4.5. Tazarotene

Tazarotene is a synthetic retinoid derived from vitamin A that has proven to down modulate keratinocyte hyperproliferation, differentiation, and inflammation which are involved in the pathogenesis of NP. It has beneficial effects on the nail matrix, bed, and periungual skin. The drug is

4.6. 5-Fluorouracil

5-Fluorouracil (5-FU) is an antimitotic and antiproliferative agent, which is active against disorders with a high proliferative activity, such as psoriasis. Using topical 5-FU with 20% urea as a penetration enhancer showed good effects on NP, but inflammation, infection, onycholysis, and discoloration were observed as adverse effects **[31].**

4.7. Anthralin

Dithranol was once the most commonly used antipsoriatic topical therapy, but because of its unpleasant cosmesis, it is rarely used nowadays **[31]**.

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4.8. Calcineurin inhibitors

Calcineurin inhibitors have a profound inhibitory effect on T-cell functions that are implicated in the pathogenesis of psoriasis. Topical tacrolimus 0.1 % ointment shows much better skin and nail penetration. It demonstrated good activity on nail bed and matrix psoriasis after 12 weeks **[32].**

4.9. Topical combination therapy

Combination formulations of topical medication can increase the effectiveness of available treatments. The combination of vitamin D analogs and corticosteroids into fixed two-compound topical formulations has increased the efficacy compared with either drug administered alone or even with non-fixed formulations of the active ingredients used in combination with each other. A single daily dose of combined betamethasone dipropionate and calcipotriene is one of the most effective topical treatment for NP **[33].**

4.10. Alternative therapy

Studies indicated that indigo naturalis (Chinese herb) regulates proliferation and differentiation of epidermal keratinocytes, restores the epidermal barrier function, and inhibits inflammatory reactions **[34].**

(Lin et al., [35])showed that Lindioil (indigo naturalis oil extract) is a safe and effective alternative topical therapy for psoriatic nails. Lindioil had the greatest effects on onycholysis and subungual hyperkeratosis, which arise from hyperproliferation, hyperkeratosis, and parakeratosis of the nail bed.

4.11. Intralesional therapy

a) Intralesional steroid

Intralesional injections are another type of local treatment. Triamcinolone acetonide 10 mg/ml is the mainstay intralesional agent used bimonthly. The procedure should be preceded by ring block or distal block anesthesia if the injection is likely to enter the matrix as this is a very sensitive site. Intralesional corticosteroids is by far the most often performed, either by injection with a needle or by the dermojet .The latter can offer an alternative application technique with considerably decreased pain **[36].**

b) Intralesional methotrexate

Methotrexate (MTX) is a folic acid antagonist that blocks DNA synthesis. Several studies reported successful treatment of NP with low dose intralesional MTX with significant reduction in NAPSI score. Mild adverse effects were recorded. Intralesional MTX was also used for perimatrical and nail bed injections with acceptable results, significant reduction in the mean NAPSI from baseline with only mild adverse events, such as pain with injection, subungual hemorrhage, pinpoint hemorrhage at the injection site, and hyperpigmentation **[37]**

4.12. Systemic Treatments

Systemic therapy with methotrexate, cyclosporine and acitretin serves as conventional treatment for the NP. In the long term, they can cause organ toxicities **[38].**

a) Methotrexate

As an orally or subcutaneously administered systemic compound, methotrexate is one of the most used systemic treatments in Plaque psoriasis, PsA, and NP. Methotrexate inhibits the T-cell proliferation and its efficacy for NP has also been demonstrated. It is cost effective and its efficacy has been known for many years. A wide range of potential side effects limit its use, including hepatotoxicity, ulcerative stomatitis, lymphopenia, nausea, low white blood cell count, and nausea. **[39].**

b) Cyclosporine

Cyclosporine is an immunosuppressant drug acts by preventing dephosphorylation of nuclear factor of activated T cell by inhibiting calcineurin phosphatase enzyme. It also exerts direct effect on keratinocyte proliferation through inhibition of calcineurin thus serving as an effective therapy for psoriasis treatment **[31].**

c) Acitretin

Acitretin a pharmacologically active metabolite of etretinate has also proved its potential for psoriasis treatment. Significant improvement of a case with severe disabling NP with oral acitretin 25 mg/day

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was observed after 6 months of treatment. The use of oral acitretin supported with urea nail lacquer, may provide good results in severe NP **[40].**

d) Apremilast

Apremilast is an oral, small-molecule inhibitor of phosphodiesterase 4 that alters the expression of a variety of immune mediators. **(Rich et al**., **[25])** demonstrated efficacy of apremilast in reducing severity of nail and scalp psoriasis.

Because apremilast is generally well tolerated and has no need for biochemical follow-up, it may be an attractive choice for patients whom systemic treatments are indicated. The very high costs of treatment may limit its use in many patients **[41].**

d) Miscellaneous Systemic Therapies

Fumaric acid esters (FAEs), sulfasalazine, and leflunomide have also been reported to be effective in NP. FAEs have little efficacy in NP, but one case has been reported in which it was effective both on nail bed and nail matrix psoriasis. Sulfasalazine and leflunomide are used to treat PsA. One prospective study assessed the clinical effectiveness and safety of leflunomide in patients with PsA, and also in psoriatic nail disease **[42].**

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