Treatment of Nail Psoriasis

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KEYWORDS

• Nail • Psoriasis • Inflammatory • Therapeutics • Targeted • Biologics • Topical • Intralesional

KEY POINTS

- Available therapies for nail psoriasis include intralesional, topical, and systemic agents, with treatment dichotomized based on few-nail (≤3 nails) and multiple-nail (>3 nails) disease.
- Intralesional steroid injections is first-line therapy for few-nail disease with nail matrix involvement. Combination topical steroids with topical vitamin D analogues is first-line therapy for few-nail disease with nail bed involvement.
- Systemic agents, including biologic agents (tumor necrosis-α inhibitors, interleukin-17 inhibitors, interleukin-23 inhibitors, interleukin-12/23 inhibitors), small molecule inhibitors (phosphodiesterase-4 inhibitors, Janus kinase inhibitors), and classical systemic immunomodulators (methotrexate, cyclosporine, acitretin), are treatment options for patients with multiple-nail disease, extensive cutaneous involvement, psoriatic arthritis, or significant impact on quality of life.

INTRODUCTION

Nail findings are a common manifestation of psoriasis that may occur in isolation or in conjunction with skin and/or joint involvement.[1] Isolated nail psoriasis (NP) is defined as nail changes in absence of cutaneous psoriasis or with limited body surface involvement (<5%), and affects 5% to 10% of all patients with psoriasis.[2] Nail involvement occurs in up to 40% and 80% of patients with cutaneous psoriasis (PsO) and psoriatic arthritis (PsA), respectively, at any one time, with an overall 80% to 90% lifetime incidence.[2] Clinical manifestations include nail matrix signs (nail plate pitting, leukonychia, red lunula, nail crumbling) and nail bed signs (onycholysis, subungual hyperkeratosis, salmon patches/oil spots, splinter hemorrhages) (**Fig. 1**).[3] NP affects the fingernails more frequently than toenails, and most often the dominant hand thumbnail and nails associated with hand function.[3] Impact of NP symptoms extend beyond aesthetics alone, with significant associated disease burden and impact on quality of life, including pain, functional restrictions, and psychosocial impairment.[4] Notably, Psoriasis Area Severity Index and Dermatology Life Quality Index scores are higher in patients with psoriasis with nail involvement compared with those without ($P < .001$).[4] Because correlation between NP and progression to PsA is well-established, all patients diagnosed with NP should undergo baseline PsA screening.[5,6] Prompt initiation of treatment of NP is crucial to prevent disability, especially because nail disease may be more resistant to treatment than PsO.

Available therapies for NP include topical therapies, intralesional injections, and systemic agents (**Box 1**).[7,8] Specific treatment selection should be individualized based on extent and severity of nail disease, presence of skin/joint involvement, safety profiles, patient lifestyle and preference, quality of life impact, patient adherence to medication regimens, and cost/insurance reimbursement factors.[9–11] Combination therapies targeting different disease pathways simultaneously may often be required for efficacy.[7] Expert consensus treatment guidelines were most recently published by Rigopoulos and colleagues[3] in 2019, because of a paucity of psoriatic clinical trials specifically measuring nail outcomes as primary end points.[3] These guidelines emphasize dichotomization of treatment based on few-nail (≤3 nails) and multiple-nail (>3 nails) disease, and nail matrix and/or nail bed involvement (**Fig. 2**).[3]

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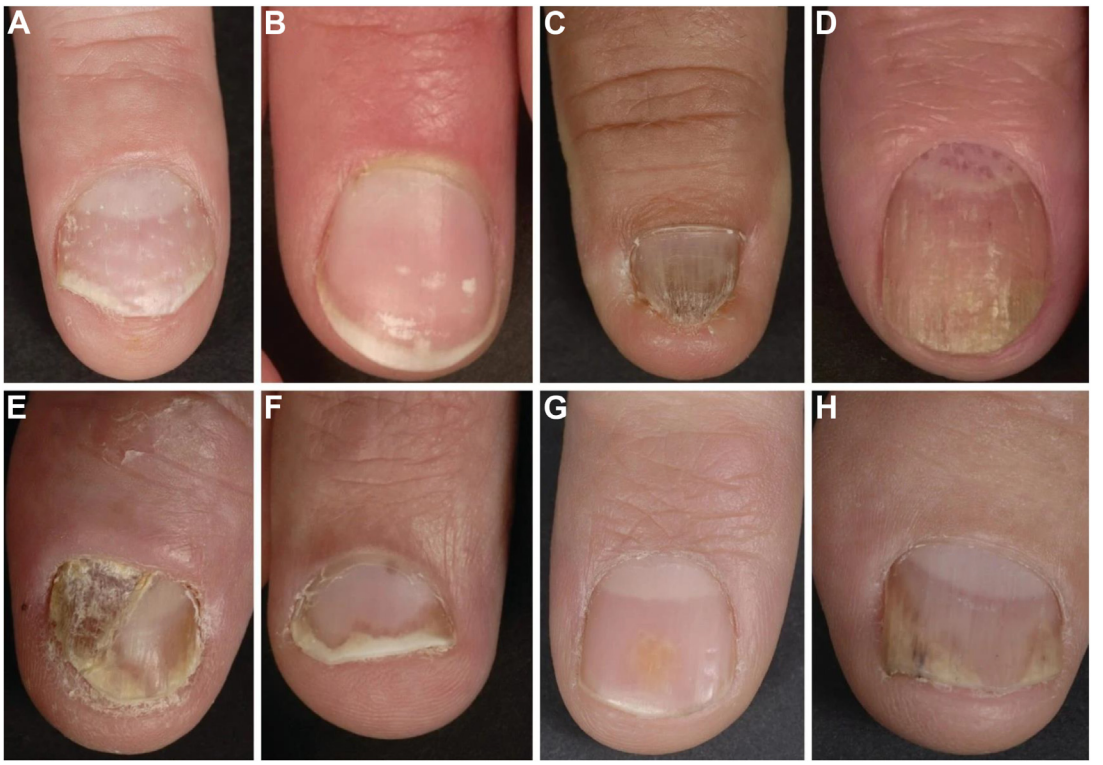

Fig. 1. Psoriasis of the nail matrix presenting as (*A*) pitting, (*B*) leukonychia, (*C*) thickening, (*D*) red spots of the lunula, and (*E*) crumbling of the nail plate. Psoriasis of the nail bed demonstrating (*F*) onycholysis, (*G*) oil-drop discoloration, and (*H*) splinter hemorrhages involving the distal third of the nail plate often embedded in subungual hyperkeratosis and/or onycholysis.[16]

For few-nail disease with nail matrix involvement only, intralesional steroid injections is recommended as first-line therapy, with combination therapy of topical steroids and topical vitamin D analogues as an alternative first-line option.[3] Second-line therapies include monotherapy with topical steroids, topical vitamin D analogues, topical retinoids, or topical tacrolimus.[3] For few-nail disease with nail bed involvement only, topical steroids alone or in combination with vitamin D analogues are first-line, with alternative options including topical vitamin D analogues, topical retinoids, topical tacrolimus, or intralesional steroid injections.[3] For involvement of matrix and bed, either intralesional steroid injections or combination topical steroid with vitamin D analogues can be used as first-line agents.[3] Systemic therapies should be considered in cases of multiple-nail disease, extensive cutaneous or joint involvement, or significant impact on quality of life.[12–14] These include biologic agents (tumor necrosis factor-α [TNF-α] inhibitors, interleukin [IL]-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors), small molecule inhibitors (phosphodiesterase-4 inhibitors, Janus kinase [JAK] inhibitors), and classical systemic immunomodulators (methotrexate, cyclosporine, acitretin).[15] Herein, we discuss efficacy and safety of therapeutic agents studied for NP, in guiding physicians in selection of specific treatment options.

DISCUSSION

Intralesional Therapies

Intralesional steroids

Intralesional corticosteroid injections is a first-line treatment option with high efficacy and safety for few-nail disease with limited or no skin involvement.[3] It is especially effective for NP with nail matrix features.[16] A single injection into the proximal nail fold allows for direct drug delivery to the nail matrix.[16] Nail bed injections also have moderate efficacy for nail bed disease, but are more painful than matrix injections.[8] A suggested maximum of 0.1 to 0.5 mL of 2.5 to 10 mg/mL of triamcinolone acetonide may be used per affected nail, with injections repeated every 4 to 8 weeks and clinical response expected within three to six sessions.[3] Ethyl chloride spray, topical anesthetic creams, air-cooling devices, vibratory devices, and/or

Box 1
List of medications studied for treatment of nail psoriasis

Intralesional agents
- Triamcinolone acetonide[a]
- Methotrexate
- 5-Fluorouracil
- Cyclosporine
- Secukinumab

Topical agents
- Steroids
  - Clobetasol propionate[a]
  - Betamethasone dipropionate[a]
- Vitamin D analogues
  - Calcipotriol[a]
  - Calcitriol[a]
  - Tacalcitol[a]
- Retinoids
  - Tazarotene[a]
  - Tretinoin
- Keratolytic agents
  - Urea nail lacquer[a]
  - Salicylic acid[a]
- Calcineurin inhibitors
  - Tacrolimus[a]
  - Cyclosporine
- 5-Fluorouracil

Systemic agents
- Biologic agents
  - Tumor necrosis factor-α inhibitors
    - Adalimumab[a]
    - Certolizumab pegol[a]
    - Etanercept[a]
    - Golimumab[a]
    - Infliximab[a]
  - Interleukin-17 inhibitors
    - Ixekizumab[a]
    - Brodalumab
    - Secukinumab[a]
    - Bimekizumab[b]
    - Netakimab[b]
  - Interleukin-12/23 inhibitors
    - Ustekinumab[a]
  - Interleukin-23 inhibitors
    - Guselkumab[a]
    - Tildrakizumab
    - Risankizumab
- Small molecule inhibitors
  - Janus kinase inhibitors
    - Tofacitinib[a]
    - Deucravacitinib
  - Phosphodiesterase-4 inhibitors
    - Apremilast[a]
- Classical systemic therapies
  - Acitretin[a]
  - Cyclosporine[a]
  - Methotrexate[a]

[a]Previously recommended by Rigopoulos and colleagues guidelines in 2019.[b]Emerging agent for treatment of nail psoriasis.

talkesthesia may be used to minimize pain during injections.[8,17,18]

Efficacy of intralesional steroid injections was demonstrated in a randomized clinical trial (RCT) of 16 patients with NP comparing one to two treatments of intralesional triamcinolone acetonide (ILTAC) 10 mg/mL versus topical clobetasol 0.05% twice a day without occlusion for 4 months.[19] There was greater reduction in target Nail Psoriasis Severity Index (NAPSI) in the ILTAC group at the second and fourth months (P = .003). An open-label trial of 19 patients with NP receiving ILTAC 10 mg/mL for a mean 1.2 doses demonstrated a 100%, 94%, 83%, 50%, and 45% improvement in subungual hyperkeratosis, transverse ridging, nail thickening, onycholysis, and pitting, respectively, at mean 9.4 months follow-up.[20] Lower concentrations of 2.5 to 5 mg/mL have similarly demonstrated high efficacy in an open-label study including six patients with NP treated monthly for 6 months.[21] Further research is needed to determine optimal dosing, dilution, number, and frequency of intralesional corticosteroid injections for NP.[3]

Safety profile of intralesional steroid injections for NP is overall favorable.[8] Possible side effects include self-limited subungual hematoma; short-term paresthesia; focal pain; periungual hypopigmentation; and more rarely, reversible atrophy at the injection site.[8,16] With appropriate technique, minimal adverse events (AEs) should occur, with little to no risk of systemic toxicity.[3] ILTAC is the only intralesional treatment that has shown safety in pregnant, pediatric, and older patients.[8]

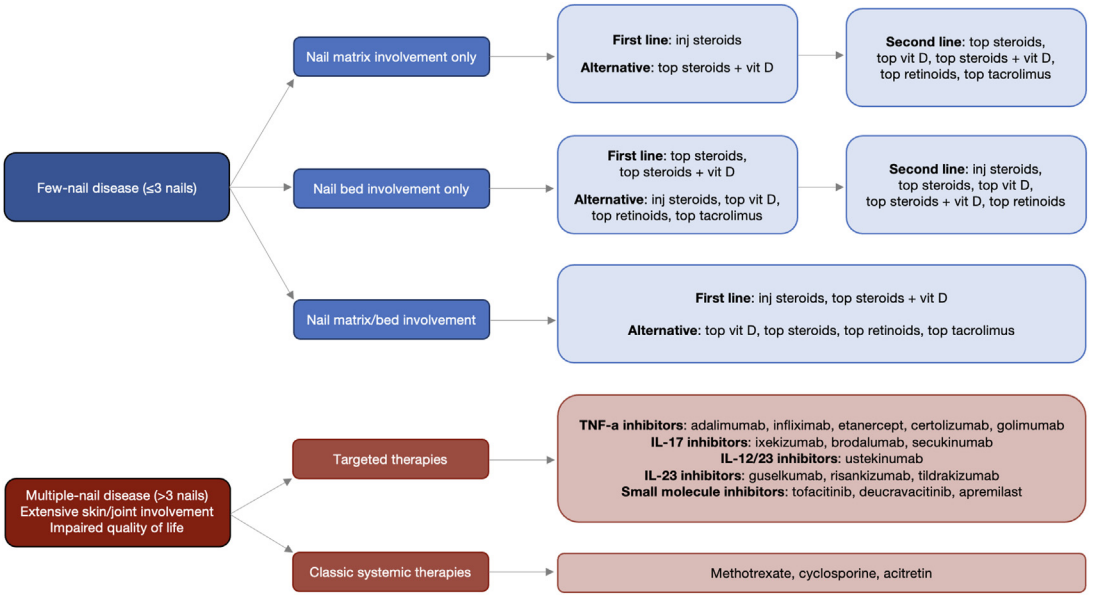

Fig. 2. Nail psoriasis treatment algorithm, updated from 2019 expert consensus guidelines.[3] Inj, injectable; top, topical; vit D, vitamin D analogues. Note: All listed targeted and classical systemic therapies are systemic agents.

Other intralesional agents

Intralesional methotrexate, a folic acid antagonist with anti-inflammatory and immunosuppressive properties, has also been studied for NP treatment.[8] An open-label trial of 12 patients with NP receiving intralesional methotrexate 25 mg/mL or ILTAC 10 mg/mL to the matrix and/or bed every 6 weeks demonstrated greater decrease in mean NAPSI score with methotrexate than ILTAC at 6 months (5.0 vs 3.5, significance not reported).[22] The only AE reported in the methotrexate group was subungual hematoma in one patient. In the ILTAC group, three patients had proximal nailfold hypopigmentation and/or subungual hematoma. Methotrexate may be used as an alternative to ILTAC, but further RCTs are needed to better understand efficacy and safety for intralesional use.

Other intralesional agents studied for NP include 5-fluorouracil and cyclosporine.[23,24] An RCT of 60 patients with NP comparing intralesional 5-fluorouracil 50 mg/mL, ILTAC 10 mg/mL, intralesional methotrexate 25 mg/mL (to the matrix and/or bed), and topical calcipotriol 0.005%/urea 20% monthly demonstrated less improvement in mean NAPSI score with 5-fluorouracil compared with ILTAC, methotrexate, and calcipotriol/urea at 3 months (29.6 ± 14 vs 44.2 ± 32.7 vs 37.7 ± 14.2 vs 57.1 ± 26.4, respectively; $P = .016$).[23] AEs of subungual hematoma and proximal nailfold hyperpigmentation were observed in one patient each in the 5-fluorouracil group. An open-label trial of 17 patients with NP comparing intralesional cyclosporine 50 mg/mL with ILTAC 10 mg/mL and methotrexate 25 mg/mL to the nail matrix every 6 weeks demonstrated less improvement with cyclosporine (percentage of nails achieving >75% improvement of mean NAPSI score [NAPSI75], 33.3%) than with ILTAC or methotrexate (NAPSI75, both 50.0%) at 6 months.[24] Cyclosporine, notably, also had more associated side effects compared with the other groups, including severe pain, short-term paresthesia, proximal onycholysis, splitting, and nail plate distortion, each occurring in one patient.

Intralesional secukinumab has also been studied in an open-label trial of six patients with NP.[25] Secukinumab at a concentration of 7.5 mg/mL, 15 mg/mL, and 30 mg/mL, injected in the nail matrix of one nail every 2 weeks, demonstrated 76.1%, 66.1%, and 75.7% improvement, respectively, in mean NAPSI score at 3 months. Clinical efficacy for nail bed disease was superior to that of nail matrix disease (88.7% vs 63.1% improvement; $P < .05$), with no AEs reported. Further trials are needed to compare outcomes with that of ILTAC, especially in terms of nail bed outcomes.

Topical Therapies

Topical steroids

Topical steroids are first-line treatment of NP with few-nail disease isolated to the nail bed, and second-line treatment of few-nail disease isolated to the nail matrix.[3] They are the most frequently used topical medication for NP treatment, with success of topical agents largely dependent on

nail unit penetrability.[7,16] Superpotent steroids, such as clobetasol propionate or betamethasone dipropionate, in ideally ointment or solution form should be used, with application once or twice daily under occlusion.[3] Treatment should not exceed 1 month consecutively because of risk of side effects.[16] Application to the proximal nailfold targets nail matrix psoriasis, whereas clipping the onycholytic nail plate may enhance penetrability for nail bed disease.[7] For all topical NP treatments, excellent compliance for prolonged periods is often necessary for complete efficacy, which may be difficult to achieve for some patients.[7] Nevertheless, topical agents should be considered in cases of patient preference or when other treatment alternatives are contraindicated.

Efficacy of topical steroids for treatment of NP has been largely studied as combination therapies with other topical or systemic medications, with limited clinical trials assessing monotherapy efficacy. An RCT assessing treatment of 46 patients with NP with clobetasol propionate 0.05% cream or tazarotene 0.1% cream monotherapy daily under occlusion demonstrated significant time-effect improvement with clobetasol for pitting, onycholysis, hyperkeratosis, and salmon patches at 6 months ($P < .001$ vs baseline).[26] Combination of topical steroids with keratolytic agents (urea nail lacquer, salicylic acid) has also demonstrated high efficacy, allowing for targeting of two disease pathways, with steroid effects simultaneously decreasing inflammation caused by keratolytic agents.[7] An RCT (n = 58 patients with NP) assessing betamethasone dipropionate 64 mg/g with salicylic acid 0.03 g/g versus calcipotriol 50 μg/g ointment twice daily demonstrated a 49.2% reduction in subungual hyperkeratosis after 5 months for the betamethasone/salicylic acid group ($P < .001$ vs baseline).[27]

Safety of topical steroids is overall favorable, with only mild side effects reported.[7] Telangiectasia or atrophy of the skin or underlying phalanx may develop with prolonged used.[16] Strict reevaluation of treatment benefit and AE risk should be performed, especially with continuous daily use.

Combination topical steroids with topical vitamin D analogues

Topical formulations containing vitamin D_3 (calcitriol) or vitamin D analogues (calcipotriol, tacalcitol) have been used for NP treatment, with calcipotriol being the most widely investigated agent among the three.[16] They regulate epidermal cell proliferation and differentiation, suppressing the production and release of proinflammatory cytokines implicated in psoriatic pathogenesis.[16] Combination topical steroids with topical vitamin D analogues is a first-line treatment option for few-nail disease with involvement of either nail matrix and/or bed.[3] Vitamin D analogues as monotherapy can also be used as a second-line treatment option.[3]

An open-label trial (n = 62 patients with NP) of combination calcipotriol cream daily on weekdays with clobetasol propionate daily on weekends demonstrated a mean 72.3% and 69.9% reduction of fingernail and toenail hyperkeratosis, respectively, at 6 months.[28] A combination calcipotriol/betamethasone dipropionate two-compound ointment demonstrated a 72% improvement in mean NAPSI score after 3 months of daily use in 25 patients with NP.[29] Calcipotriol 50 μg/g ointment used twice daily as monotherapy showed significant clinical improvement at 5 months in 14 of 24 patients with NP studied.[30] Calcipotriol was particularly effective for subungual hyperkeratosis, onycholysis, and discoloration. Safety is overall favorable, with minimal AEs of fingertip tenderness and irritation reported in calcipotriol clinical trials.[29,30]

Topical retinoids

Topical retinoids, namely tazarotene, have been recommended as an alternative first-line NP treatment of few-nail disease of the nail bed, and second-line option for nail matrix involvement.[3] Tazarotene is hydrolyzed to tazarotenic acid when applied topically, binding selectively to retinoic acid receptors β and γ, with antiproliferative and anti-inflammatory effects.[3,16] It is most commonly used at a concentration of 0.1% in gel, ointment, or cream form, applied daily under occlusion for 3 to 6 months.[16]

Treatment with tazarotene 0.1% gel under occlusion was superior to placebo vehicle gel for reduction of onycholysis and pitting at 6 months ($P < .05$), in an RCT including 31 patients with NP.[31] An RCT (n = 46 patients with NP) comparing tazarotene 0.1% cream versus clobetasol propionate 0.05% cream monotherapy daily under occlusion demonstrated significant time-effect improvement at 6 months ($P < .001$ vs baseline), with no significant differences between the two agents.[26] Tazarotene is overall tolerable, with potential mild side effects of erythema, irritation, dryness, desquamation, and paronychia, and two cases of periungual pyogenic granuloma reported.[16,32] Studies have suggested that tazarotene seems to lack efficacy in treating nail matrix psoriasis compared with other agents.[7]

Topical tretinoin, another retinoid compound, has shown efficacy in a case report of a 12-year-old girl with NP.[33] Treatment with 0.025% cream applied daily resulted in an 80% reduction in NAPSI score at 3 months, with the only AE being mild dryness at the fingertips.

Topical calcineurin inhibitors

Calcineurin inhibitors, including tacrolimus, have also been studied for topical NP treatment, and are considered as an alternative first-line agent for few-nail disease of the nail bed and second-line agent for nail matrix disease.[3] Tacrolimus inhibits IL-2 transcription and T-cell signal transduction, reducing inflammation and epidermal hyperproliferation.[16] Use of systemic tacrolimus is often limited by side effects, and topical treatment limits AEs. However, data on efficacy for NP are sparse. An RCT assessing efficacy of tacrolimus 0.1% ointment daily without occlusion, applied to the nails of one hand with the other hand used as a control, demonstrated a mean 57% decrease in NAPSI score after 3 months in treated versus untreated nails ($P < .001$).[34] Acute paronychia was the only AE reported, noted in one patient. Overall, topical tacrolimus is associated with only mild side effects, and may be considered for patients with skin atrophy secondary to prolonged steroid use.[7] However, it may have lower penetrance compared with other agents, because of its lipophilic nature.[7]

Cyclosporine has been studied for NP treatment, but was not included in guideline recommendations by Rigopoulos and colleagues.[3] Topical oil-dissolved 70% cyclosporine solution compared with oil alone applied twice daily in an NP RCT (n = 8) demonstrated a mean 77% improvement in the cyclosporine-treated group (pitting, hyperkeratosis, onycholysis, crumbling, and oil-drop discoloration).[35] There were no reported AEs. Cyclosporine may have less nail plate penetration compared with tacrolimus.[7]

Other topical agents

5-Fluorouracil has been studied in topical formulations for NP treatment, but was not included in the previously mentioned consensus guidelines.[3] It is a chemotherapeutic agent with antimitotic and cytotoxic effects, showing variable results for NP when used topically.[16] An open-label study assessing 1% 5-fluorouracil/urea 20% liquid twice daily in 59 patients with NP demonstrated a mean 50% improvement in oil spots and subungual hyperkeratosis at 6 months.[36] An RCT comparing 1% 5-fluorouracil in urea/propylene glycol vehicle with urea/propylene glycol vehicle demonstrated significant improvements in Nail Area Severity score for both groups ($P < .05$ vs baseline), but with no differences between groups ($P = .063$).[37] Inflammation, infection, onycholysis, and yellow nail discoloration are reported side effects with topical 5-fluorouracil use.[16,38] Overall, it is used infrequently because of variable efficacy and high rate of AEs.[38]

Classical Systemic Therapies

Methotrexate

Methotrexate is a classical systemic immunomodulator that has demonstrated moderate efficacy for NP treatment.[15] It competitively inhibits dihydrofolate reductase and decreases proliferation of lymphoid cells, with immunosuppressive effects.[39] Systemically, it may be administered orally or as a subcutaneous, intramuscular, or intravenous injection. Recommended dosing is up to 15 mg weekly with folic acid, until at least moderate improvement.[3] Reduced dosages may be used for maintenance.[3] Efficacy for NP was demonstrated in an RCT (n = 37 patients with NP) comparing oral methotrexate 15 mg weekly and cyclosporine 5 mg/kg daily.[40] Patients treated with methotrexate demonstrated a 43.3% reduction in mean NAPSI score at 24 weeks, with significant improvement in nail matrix NAPSI scores ($P = .001$ vs baseline). The METOP RCT (n = 59 patients with NP) assessed methotrexate treatment subcutaneously dosed at 17.5 mg weekly, demonstrating a 21.5% reduction and 45.8% reduction in mean NAPSI score at Week 16 and 52, respectively.[41] Methotrexate exhibits a wide range of AEs, including ulcerative stomatitis, leukopenia, nausea, abdominal distress, myelosuppression, and hepatotoxicity.[8] It is a known teratogen, and thus contraindicated in pregnancy.[15] Side effects, numerous contraindications, and need for baseline and follow-up monitoring may limit its use.[15]

Cyclosporine

Cyclosporine is an immunomodulatory drug that has efficacy for NP treatment when administered systemically.[15] It is a calcineurin inhibitor that prevents upregulation of IL-2 and subsequent T-cell activation.[3] Recommended dosing for NP is 3 to 5 mg/kg daily until at least moderate improvement, and should only be used for short-term treatment (<6–12 months).[3,16] Efficacy for nail outcomes was demonstrated in an open-label trial (n = 18 patients with NP) treated with cyclosporine 2.5 to 3.75 mg/kg daily, with 44% of patients demonstrating at least 50% improvement in NAPSI score after 12 months.[42] Oral cyclosporine at 3.5 mg/kg daily used in combination with topical calcipotriol cream twice daily demonstrated a 79% improvement in NP features of subungual hyperkeratosis, onycholysis, and pitting (n = 54 patients with NP).[43] An RCT comparing oral methotrexate 15 mg weekly and cyclosporine 5 mg/kg daily in 37 patients with NP demonstrated a 37.2% improvement in mean NAPSI score in cyclosporine-treated patients, with significant improvement seen for nail bed NAPSI scores ($P = .001$ vs baseline).[40] Use is limited by

serious AEs, including nephrotoxicity, hypertension, headache, paresthesia, and myalgia.[15] Frequent drug interactions and need for baseline and follow-up monitoring may limit use.[15]

Acitretin

Systemic acitretin, a retinoic acid modulator with anti-inflammatory effects, has shown moderate efficacy for NP.[15] Recommended dosing is 0.2 to 0.4 mg/kg daily for greater than 6 months or until at least moderate improvement.[3] Acitretin may be less effective than other conventional systemic agents.[16] Efficacy was assessed in an open-label trial including 36 patients with NP, demonstrating 41% reduction in mean NAPSI score after 6 months.[44] Common AEs include xerosis, xeropthalmia, xerostomia, cheilitis, and skin itching or burning, with alopecia, dermatitis, and pyogenic granulomas reported with long-term treatment.[15] It is a known teratogen, and thus contraindicated in pregnancy. Pregnancy must be avoided for at least 3 years following treatment cessation.[15] As with other classical systemic therapies, baseline screening and ongoing monitoring is required.[15]

Targeted Therapies

The advent of targeted therapies, including biologic treatments and small molecule inhibitors, has revolutionized treatment of psoriasis, with high efficacy demonstrated for nail outcomes.[14] These therapies should be considered for patients with greater than three nails involved, extensive cutaneous or joint involvement, significant impact on quality of life, and/or failure of other treatments.[3]

Tumor necrosis factor-α inhibitors

TNF-α inhibitors, including adalimumab, infliximab, etanercept, certolizumab, and golimumab, are the most long-standing class of biologics for psoriasis treatment and have demonstrated efficacy for NP.[14] Blockade of TNF-α proinflammatory cytokines decreases promotion of inflammatory infiltrate and induction of keratinocyte proliferation.[16]

Adalimumab's efficacy was assessed in a phase III RCT, with 217 patients with NP demonstrating 44.2% and 56.2% reduction in mean NAPSI score at Weeks 16 and 26, respectively, superior to placebo at both timepoints ($P < .001$).[45] Infliximab's efficacy for NP was demonstrated in the EXPRESS phase III RCT, with 302 patients with NP demonstrating a mean 26.0% and 56.3% decrease in mean target NAPSI score at Weeks 10 and 24, respectively, both superior to placebo ($P < .001$).[46] In the LIBERATE phase III RCT, etanercept demonstrated a 37.7% reduction in mean NAPSI score compared with placebo at Week 16 ($P = .0024$).[47] Certolizumab was studied in the phase III RAPID-PsA RCT, with 300 patients with NP demonstrating 51.6% reduction in mean modified target NAPSI score compared with placebo at Week 24 ($P < .001$).[48] The GO-VIBRANT phase III RCT (n = 367 patients with NP) assessing efficacy of golimumab demonstrated 51.6% and reduction in mean modified NAPSI score at Weeks 14 and 24, respectively, both superior to placebo ($P < .0001$).[49] In comparing the TNF-α inhibitor agents, a prospective comparative study of 60 patients with NP demonstrated a greater reduction of mean NAPSI score at Week 14 in patients treated with infliximab than with adalimumab or etanercept (55.6% vs 34.8% vs 33.6%, respectively; $P < .05$).[50] Likewise, in a meta-analysis including 11 NP clinical trials found that, among included targeted therapies, infliximab demonstrated the second highest improvement in weighted mean difference (WMD, 46.2%) of NAPSI score at Weeks 10 to 16, preceded only by tofacitinib (WMD, 56.7%).[51] At Weeks 24 to 26, infliximab likewise demonstrated the second highest improvement (WMD, 56.9%) among included agents, inferior only to ixekizumab (59.4%).

Potential side effects for TNF-α inhibitors include upper respiratory infections (URI), nasopharyngitis, headache, diarrhea, injection site reactions, and mild transaminitis.[14,15] Rarer but serious side effects include activation of opportunistic infections (including tuberculosis), congestive heart failure, demyelinating diseases, drug-induced lupus, and serious hypersensitivity reactions.[15] Malignancies, particularly lymphoma, have been reported in clinical trials, but most evidence does not point to a significantly increased malignancy risk with TNF-α inhibitor use.[15] Of available biologic agents, TNF-α inhibitors have the most data demonstrating no direct evidence of teratogenicity, embryotoxicity, or fetotoxicity, and are thus regarded as safe during pregnancy.[15]

Interleukin-17 inhibitors

IL-17, including ixekizumab, brodalumab, and secukinumab, are another class of biologic agents used for NP treatment.[14] IL-17 is a T-cell-derived cytokine with skin-altering functions, and its blockade inhibits psoriatic disease.[16]

Ixekizumab was studied in the SPIRIT-P1 phase III RCT (n = 289 patients with NP), demonstrating 65.7% reduction in mean NAPSI score at Week 24 ($P < .001$ vs placebo).[52] Ixekizumab was superior to adalimumab at Week 24 (SPIRIT-H2H), to ustekinumab at Weeks 8, 24, and 52 (IXORA-S), and to etanercept at Week 12 (UNCOVER-1/2/3).[53–55] Ixekizumab also demonstrated the most improvement in WMD (59.4%) of NAPSI score at Weeks 24 to 26, among studied targeted agents in a meta-analysis of 11 NP clinical trials.[51]

Brodalumab has demonstrated superiority to ustekinumab in the AMAGINE-2 and AMAGINE-3 phase III RCTs (n = 283 patients with NP), with a 43.7%, 76.9%, and 82.4% reduction in mean target NAPSI score at Weeks 12, 24, and 36, respectively, superior to ustekinumab at all three time points ($P < .05$).[56] Secukinumab's efficacy for NP was demonstrated in the TRANSFIGURE phase III RCT (n = 198 patients with NP), with a 45.3% reduction in mean NAPSI score compared with placebo at Week 16 ($P < .0001$).[57]

Potential side effects of IL-17 inhibitors include injection site reactions, nasopharyngitis, URI, diarrhea, mucocutaneous candidiasis, and neutropenia.[14,15] Exacerbation of inflammatory bowel disease with IL-17 inhibitor use has been reported in clinical trials assessing patients with inflammatory bowel disease, but risk for patients with psoriasis is unknown.[15] Rare but serious side effects include activation of opportunistic infections (including tuberculosis) and hypersensitivity reactions.[15]

Interleukin-12/23 inhibitors

Ustekinumab, a dual IL-12 and IL-23 inhibitor, and strictly IL-23 inhibitors, including guselkumab, risankizumab, and tildrakizumab, have demonstrated efficacy for NP treatment.[14] Inhibition of IL-12 and IL-23 cytokines blocks differentiation and expansion of Th1 and Th17 populations associated with psoriasis pathogenesis.[16]

Ustekinumab's efficacy for nail outcomes was demonstrated in the PHOENIX-1 phase III RCT (n = 545 patients with NP), with 26.7% reduction in mean target NAPSI score at Week 12 ($P < .001$ vs placebo).[58] Two phase III RCTs for plaque psoriasis (VOYAGE-1/2) assessed efficacy of guselkumab compared with adalimumab and placebo (n = pooled 1044 patients with NP).[59] Guselkumab-treated patients demonstrated a 37.5% and 52.9% reduction in mean target NAPSI score at Weeks 16 and 24, both superior to placebo ($P < .001$), with comparable efficacy to that of adalimumab-treated patients. Risankizumab demonstrated a 54.1% reduction in mean modified NAPSI score at Week 24 ($P < .001$ vs placebo) in the KEEPsAKE-1 phase III RCT with 647 patients with NP.[60] Tildrakizumab's efficacy for NP treatment has not yet been assessed in RCTs, but demonstrated a 72.7% reduction in mean fingernail Physician Global Assessment (PGA-F) score at Week 52 in the prospective observational TILOT study (n = 411 patients with NP).[61] In two comparative studies, guselkumab, risankizumab, and tildrakizumab demonstrated comparable NAPSI outcomes at Weeks 16, 28, and 52, but larger trials are needed to corroborate these findings.[62,63] Because these agents are among the newer approved biologics for psoriasis, further trials are needed to fully establish efficacy compared with that of other agent classes.

Potential side effects for IL-12/23 inhibitors include nasopharyngitis, URI, headaches, and arthralgia.[14,15] A network meta-analysis of 52 clinical trials including 16 systemic treatments for psoriasis demonstrated that IL-23 inhibitors had the lowest rate of AEs at Weeks 12 to 16 and most favorable benefit-risk profile at Weeks 48 to 56, among studied agents.[64] Rarer but serious side effects may include increased risk of malignancies and hypersensitivity reactions.[15]

Small molecule inhibitors

Tofacitinib is a JAK inhibitor that downregulates the JAK-STAT pathway and reduces psoriatic inflammatory responses.[14] Efficacy for NP was demonstrated in the OPT PIVOTAL-1/2 phase III RCTs (n = pooled 1196 patients with NP), with 34.3% reduction in mean NAPSI score after 16 weeks ($P < .0001$ vs placebo).[65] Of studied targeted agents in a meta-analysis of 11 NP clinical trials, tofacitinib demonstrated the greatest improvement in WMD (56.7%) of NAPSI score at Weeks 10 to 16.[51] Deucravacitinib is another JAK-STAT pathway inhibitor that specifically targets tyrosine kinase 2.[14] Of 184 patients with NP in the POETYK PSO-1/2 phase III RCTs, 20.5% achieved a PGA-F score of 0 to 1 at Week 16 ($P = .0272$ vs placebo), and 51.7% at Week 52.[66] Further studies are needed to fully establish efficacy of deucravacitinib for NP. Potential side effects of JAK inhibitors include URI, nasopharyngitis, diarrhea, and headache, and rare incidences of serious infections and malignancies.[15] There is increased risk of herpes zoster infection and hyperlipidemia.[15]

Apremilast is a phosphodiesterase-4 inhibitor that increases intracellular cyclic adenosine monophosphate and subsequently downregulates inflammatory pathways.[14] The ESTEEM-1 phase III RCT demonstrated 22.5% reduction in mean target NAPSI score at Week 16 in 558 patients with NP ($P < .0001$ vs placebo).[67] Efficacy of apremilast is comparatively lower than that of other biologic treatments, but is also the only targeted therapy that requires no baseline laboratory testing before initiation.[14] Potential side effects include diarrhea, nausea, URI, and headache, with gastrointestinal symptoms and weight loss more common during the first month of treatment and dose-dependent.[15] Other rare but serious side effects include depression and hypersensitivity reactions.[15]

Emerging targeted therapies

Emerging therapies in the psoriatic pipeline that have shown efficacy for NP include bimekizumab

and netakimab.[14] Bimekizumab is a dual IL-17 A/F inhibitor that was approved in the European Union for PsO and PsA in August 2021, and approved in the United States for PsO in October 2023.[68] Nail outcomes were assessed in the BE RADIANT and BE SURE phase III RCTs (n = pooled 111 patients with NP), with 51.0% to 58.6% of patients achieving a modified NAPSI score of 0 at Week 52.[69] Netakimab, another IL-17 inhibitor, has shown efficacy for NP in the PLANETA phase III RCT (n = 213 patients with NP), demonstrating changes from mean baseline NAPSI of −11 and −19 at Weeks 24 and 52, respectively ($P < .0001$ vs baseline NAPSI, 14 [0–37]).[70] Further studies are needed to fully establish efficacy for NP of these newer therapies.

Overall, most RCTs assessing targeted therapy outcomes for NP have included subpopulations of patients with nail involvement among larger PsO and/or PsA cohorts.[14] Further trials specifically assessing efficacy and safety profiles for isolated patients with NP are needed, and broader inclusion and analysis of outcomes for pediatric, pregnant, and older patients, and diverse racial/ethnic groups.[71–76]

SUMMARY

Numerous intralesional, topical, and systemic agents have been studied for treatment of NP. For few-nail disease (≤3 nails), intralesional steroid injections and combination topical steroids (high-potency) with topical vitamin D analogues are efficacious and safe first-line therapies. Other treatments, including topical retinoids and topical calcineurin inhibitors, are alternatives. For multiple-nail disease (>3 nails), extensive cutaneous or joint involvement, or cases with significant impact on quality of life, systemic treatments should be considered. Biologic agents and small molecule inhibitors are considered first-line therapy for extensive NP, whereas classical systemic immunomodulators have demonstrated moderate efficacy. Newly studied therapies for nail outcomes, and emerging targeted agents in the psoriatic pipeline, will continue to transform NP treatment.

CLINICS CARE POINTS

- Treatment of NP is dichotomized based on few-nail (≤3 nails) and multiple-nail (>3 nails) disease, and nail matrix and/or nail bed involvement.
- For few-nail disease with nail matrix involvement only, intralesional steroid injections is first-line therapy. For few-nail disease with nail bed involvement only, topical steroids (high-potency) alone or in combination with vitamin D analogues are first-line. For involvement of matrix and bed, either intralesional steroid injections or combination topical steroid (high-potency) with vitamin D analogues may be used as first-line agents. Alternative agents for few-nail disease, including topical retinoids and topical calcineurin inhibitors, may be used to avoid prolonged steroid use. Intralesional treatment is associated with pain during injections, whereas topical treatments require compliance for prolonged periods.
- Systemic therapies should be considered in cases of multiple-nail disease, extensive cutaneous or joint involvement, significant impact on quality of life, or failure of other treatments. Biologic agents and small molecule inhibitors may serve as potential first-line therapies, with high efficacy for NP. Classical systemic immunomodulators have demonstrated moderate efficacy, and may be used for patients wanting to avoid biologic treatments, for short-term therapy, or when step therapy is required.
- Treatment selection is individualized based on extent and severity of nail disease, presence of skin/joint involvement, safety profiles, comorbidities, drug-drug interactions, patient lifestyle/preference, quality of life impact, patient adherence to medication regimens, and cost/insurance reimbursement factors. Combination therapies targeting different disease pathways simultaneously may be required in some patients.

DISCLOSURE

Mr J.K. Hwang and Dr S.R. Lipner have no conflicts of interest to disclose. Dr S.R. Lipner has served as a consultant for Ortho-Dermatologics, BelleTorus Corporation, Eli Lilly, and Moberg Pharmaceuticals. Mr J.K. Hwang has no financial disclosures.

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