Running head: Management of Nail Psoriasis

Title: Nail Psoriasis: Diagnosis, Assessment, Treatment Options, and Unmet Clinical Needs

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ABSTRACT

Objective: An estimated 40%–50% of patients with psoriasis have psoriatic nail disease, which is associated with and directly contributes to a greater clinical burden and worse quality of life in these patients. In this review, we examine how recent advances in the use of new diagnostic techniques have led to improved understanding of the link between nail and musculoskeletal manifestations of psoriatic disease (eg, enthesitis, arthritis) and we review targeted therapies for nail psoriasis.

Methods: We performed a literature search to identify which systemic therapies approved for the treatment of psoriasis and/or psoriatic arthritis (PsA) have been evaluated for the treatment of nail psoriasis, either as a primary or secondary outcome. A total of 1546 articles were identified on February 18, 2019 and evaluated for relevance.

Results: We included findings from 66 articles on systemic therapies for the treatment of nail psoriasis in psoriatic disease. With several scoring systems available for the evaluation of psoriatic nail disease, including varied subtypes and application of the Nail Psoriasis Severity Index, there was a high level of methodological heterogeneity across studies.

Conclusion: Nail psoriasis is an important predictor of enthesitis, which is associated with the early stages of PsA; therefore, it is important for rheumatologists and dermatologists to accurately diagnose and treat nail psoriasis to prevent nail damage and potentially delay the onset and progression of joint disease. Further research is needed to address the lack of both standardized nail psoriasis scoring systems and well-defined treatment guidelines to improve management of psoriatic disease.
Background

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects approximately 2%–3% of the population.(1, 2) Among patients with psoriasis, an estimated 40%–50% have psoriatic nail disease, and lifetime prevalence of nail psoriasis (NP) is as high as 90%.(3-6) However, in 5%–10% of cases, NP may manifest in the absence of cutaneous symptoms.(7, 8)

Nail involvement is associated with greater severity of psoriasis(3) and is more common in patients with joint involvement. NP is an independent predictor of psoriatic arthritis (PsA).(9) The reported prevalence of NP in patients with PsA has varied between cohorts, from 32%–97% (average 66%), according to a recent systematic review.(10) NP is also associated with decreased quality of life in patients with psoriasis and/or PsA,(11, 12) may cause severe pain, and may be associated with an increased prevalence of anxiety and depression.(13) Patients with NP often have difficulty putting on shoes or socks and struggle to perform certain daily household activities, which leads to worse health-related quality of life and reduced work productivity. Because nails, especially fingernails, are highly visible and difficult to conceal, NP can cause embarrassment and self-consciousness, and many patients feel stigmatized by what is perceived as a disfiguring disease.(11, 14)

The nail is connected to underlying bone via an enthesis network that is fused with the extensor tendon crossing the distal interphalangeal (DIP) joint (Figure 1).(15) This anatomical connection of the nail matrix to the musculoskeletal system means that NP can be an early indicator of PsA;(16-19) therefore, there is a need for awareness
and understanding of nail disease among rheumatologists, primary care providers, and dermatologists to improve identification and management of PsA.

This review provides an overview of NP, discusses the use of new diagnostic techniques with a focus on the resulting improved understanding of the link between nail and musculoskeletal manifestations of psoriatic disease, and reviews the current targeted therapies for NP. Literature search details are provided in the Data Supplement.

Overview of the Nail Unit

The nail unit is composed of 4 epithelial structures—the nail matrix, the nail bed, the hyponychium, and the proximal and lateral nail folds, which function to produce, attach, and protect the nail plate (Figure 1).(5, 13) The nail matrix cells differentiate into the hard, rectangular, translucent structure we refer to as the nail plate, which is nonliving tissue and hence, technically, not part of the nail unit. The hyponychium and the lateral and proximal nail folds act as seals to prevent environmental pathogens and irritants from penetrating the nail unit and causing disease.

The primary function of the nail is to protect the digits from injury, enhance fine motor function of the digits, and to scratch in defense or to quell itch. The healthy nail plate is translucent, hard, and colorless in all people and derives its apparent color from underlying structures. The white semicircular structure in the proximal nail, called the lunula, represents the distal portion of the nail matrix seen through the proximal nail plate. The highly vascularized nail bed results in the apparent pink color of the nail; the
white free edge of the nail plate is due to air under the nail plate and explains the white
color of lifted nail plate in onycholysis.

The nail matrix produces the nail plate by differentiation of nail matrix
keratinocytes into flattened onychocytes, without the formation of keratohyalin granules.
Sheets of matrix squamous cells flatten and are closely packed in lamella of the nail
plate. Sulfurous proteins and calcium phosphate provide strength and flexibility to nail
plate keratin. The rate of nail plate growth limits the time scale over which changes can
be observed. In healthy individuals, nail elongation speed (NES) is approximately
0.1 mm/day; in people with psoriasis, NES increases by around 10%-25%.(20, 21)
The nail bed firmly attaches to the ventral aspect of the nail plate by way of parallel
longitudinal ridges and grooves that interlock with and bind the nail plate tightly to the
nail bed as it grows distally. Nail bed epithelium does not produce keratohyalin granules
and does not have a granular layer—unlike the nail folds and hyponychium, which
exhibit the keratinization typical of normal volar skin. The nail bed also contains a rich
vascular system within the parallel longitudinal grooves between the ridges, which
explains the orientation of splinter hemorrhages within the nail bed.(5, 13)

Because of the anatomy of the nail unit and its connection to the DIP joints, the
presence of NP can serve as a predictor for development of PsA, especially of extensor
tendon enthesopathy of the DIP joints.(16-19) This association has been linked to the
anatomical connection between the nail matrix and the entheses of the DIP joints
(Figure 1). The nail is anchored to underlying bone by a “mini-enthesis network,”
whereby the extensor tendon that crosses the DIP is fused with the nail matrix and nail
root.(15) This may explain why patients with PsA, who usually present with enthesitis of
the DIP joint, also frequently (although not always) present with nail changes characteristic of NP.

**Diagnosis and Assessment of NP**

**Overview**

NP can occur in all portions of the nail unit, and the clinical features of NP, such as pitting, onycholysis, and crumbling depend on which part of the nail unit is affected by the psoriatic inflammatory process (Figure 2). The symptoms of nail matrix psoriasis depend on the precise location of psoriatic disease in the proximal or distal matrix, as well as the transverse extent and duration of the disease process. Pitting, crumbling, and leukonychia are caused by foci of psoriasis pathology in the nail matrix that forms the nail plate. Other less common nail matrix features include Beau lines (deep horizontal indentations), onychomadesis (separation of the nail plate from the nail matrix), trachyonychia (rough, ridged nails), and total nail plate dystrophy.

Psoriasis in the nail bed causes oil-drop (or “salmon patch”) dyschromia, nail bed hyperkeratosis, and splinter hemorrhages—all of which disrupt nail plate attachment—and, eventually, onycholysis. Psoriasis of the proximal and lateral nail folds resembles psoriasis on other skin sites. The cuticle attachment can be destroyed by psoriasis of the nail folds, which results in nail plate surface irregularities similar to those observed in paronychia.

**Diagnosis**
NP can usually be diagnosed based on clinical features in patients with accompanying skin and/or joint symptoms of psoriatic disease.(13) In the absence of diagnosed skin or joint psoriatic disease, NP can be difficult to differentiate from other causes of nail dystrophy, and idiopathic nail dystrophy should be part of the differential diagnosis.(13, 23, 24) The clinical presentation of NP can vary greatly based on the part of the nail unit that is affected (Figure 2). NP color changes, hyperkeratosis, onychorrhexis, and nail plate thickening often resemble onychomycosis, which is frequently observed in up to 60% of patients with psoriasis. Changes in the distal or marginal nail plate can resemble lichen planus.

Biopsies can provide information on histopathologic nail changes that can inform difficult diagnoses, but nail biopsies are rarely performed because they are invasive procedures associated with bleeding, pain, permanent scarring and nail dystrophy, and increased risk for secondary infection.(24-26) Nail clippings can be analyzed to identify fungal infection, parakeratosis, and subungual hyperkeratosis.(27, 28)

Imaging techniques, including high-resolution ultrasound, dermoscopy, videodermoscopy, optical coherence tomography, capillaroscopy, and confocal laser scanning microscopy, are increasingly being used as noninvasive diagnostic tools for identifying various features of NP and response to treatment.(26, 29-33) Once NP is diagnosed, it is important for clinicians to be able to assess its severity in order to determine an optimal treatment strategy and to monitor the response to therapy.(34)

Nail Assessment and Scoring Systems
Overall clinical severity has been described using the fingernail Physician’s Global Assessment (f-PGA, or Nail PGA),(35-37) by which the fingernails are assessed for nail plate pitting, crumbling, onycholysis, oil drop discoloration, and/or nail bed hyperkeratosis on a 5-point scale, from 0 (clear) to 4 (severe), and by simple visual analog scale (VAS; used in some PsA trials). The need for more precise outcome measures to determine therapeutic efficacy in clinical trials has led to several more complex scoring systems (Table 1).

The Nail Psoriasis Severity Index (NAPSI) is the most widely used tool for scoring NP in clinical trials. Using the NAPSI, each nail is divided into 4 quadrants and scored based on the presence or absence of psoriatic changes to the nail matrix and the nail bed (Figure 3).(38, 39) The NAPSI usually assesses fingernails, for a total score of 0–80, but some studies have also included the toenails (scoring 0–160, Table 2). The NAPSI is the only system that explicitly separates nail matrix and nail bed symptoms.

A modified version of the NAPSI (mNAPSI), used in several clinical trials to date, demonstrated superior interrater variability and correlations with patient and physician global assessments.(40) Scoring of the mNAPSI is based on the whole of each fingernail, to avoid variability in defining quadrants. Four abnormalities are scored as 0 (absent) or 1 (present): leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula. Three other abnormalities are scored between 0 and 3, depending on their extent: the percentage area of onycholysis and oil-drop dyschromia (considered together as they are part of the same pathological process) is scored as 0 (none), 1 (1%–10%), 2 (11%–30%), or 3 (>30%); the number of pits is scored as 0 (none), 1 (1–
10 pits), 2 (11–49 pits), or 3 (≥ 50 pits); and the percentage area of nail plate crumbling is scored as 0 (none), 1 (1%–25%), 2 (26%–50%), or 3 (>50%).(40) The total fingernails score for mNAPSI is 0–130. By assessing the nail as a whole rather than by quadrant, the mNAPSI eliminates a source of variation, but this may reduce its sensitivity to early changes in response to treatment.

A common strategy to simplify follow-up assessments has been the use of a target nail, in which only the baseline worst affected nail is quantified at follow-up. In the original NAPSI paper, the authors suggested that a “target NAPSI” could be scored by the presence or absence of each of the 4 nail bed and 4 matrix anomalies in each quadrant of a single nail, for a score of 0–32.(39) A “modified target NAPSI” (not to be confused with mNAPSI) was subsequently proposed, in which each of the 8 nail anomalies in each quadrant were scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe); for a total score of 0–96.(41) However, neither of these more complex target nail systems are commonly used—most studies reporting data on target nails have used the regular NAPSI or mNAPSI applied to a single nail, for a score of 0–8 or 0–13 (Table 2).

Five other nail scoring systems are used less frequently: 1) the Psoriasis Nail Severity Score (PNSS),(42, 43) 2) the Baran system,(44) 3) the Cannavò system,(45) 4) the Nail Area Severity (NAS),(46) and 5) the Nijmegen-Nail psoriasis Activity Index tool (N-NAIL), which combines the elements from other systems that best predicted clinical assessments (Table 1).(34)

Scoring systems that have been developed to measure the impact of NP on quality of life include the Nail Psoriasis Quality of Life Scale (NPQ10) and the Nail...
Assessment in Psoriasis and Psoriatic Arthritis (NAPPA); however, published data on the use of these tools are extremely limited.(47-49)

Although many nail scoring systems are available, most of these instruments were developed for use in clinical trials and are typically not used in daily practice. Rheumatologists and dermatologists will usually note the presence or absence of nail lesions but may not always use objective scoring methods to evaluate the severity of nail disease or response to treatment. It should also be noted that the reliability of NAPSI when used by nonexpert rheumatologists has been shown to be variable.(50) Another option is the physician global VAS for NP, which can be performed quickly and easily by clinicians in a busy clinic, making it more likely to be used than a more time-consuming assessment tool such as NAPSI, mNAPSI, or N-Nail. Although a physician VAS does not provide the same level of detail as other tools and does not differentiate between nail matrix and nail bed pathology, it correlates strongly with the mNAPSI and has excellent internal consistency and interrater reliability.(40) Currently, there is a lack of consensus on the best NP scoring system, and most available instruments have not been completely validated or do not consider patient-specific factors such as overall burden or impact on quality of life.(34, 47)

In addition to measures evaluated by physicians, patient’s global assessments are routinely used in studies of psoriatic conditions, generally based on a VAS. Because skin and joint symptoms are not always of the same severity, it was suggested that patients with PsA be given separate joint- and skin-focused VAS.(51) Other clinicians subsequently suggested that nail symptoms should also be assessed by a separate
VAS and showed that patient’s nail global VAS scores were moderately correlated to mNAPSI (Spearman rho 0.55).(52)

Nail Manifestations as Indicators of PsA and the Importance of Imaging

Early, targeted treatment of NP is important because of the strong association between NP and the development of PsA.(16-19) Patients with NP have an almost 3-fold higher risk of developing PsA than patients with psoriasis who do not have signs of nail dystrophy.(53)

Enthesitis is typically one of the earliest inflammatory changes observed in PsA, especially in the DIP joints. Development of NP may be the first sign of joint disease resulting from subclinical enthesitis in the closely anatomically associated entheses of the DIP extensor tendons (Figures 1, 4).(18, 53-55) This hypothesis is supported by results from several recent imaging studies showing that changes in the DIP joint capsule are closely linked to histologic nail changes and diffuse inflammatory responses extending from the enthesis to the nail.(10, 15, 16, 56, 57) Specifically, patients with psoriasis with nail involvement have higher enthesopathy scores on ultrasound than patients without nail disease, as a result of entheseseal thickening of the extensor tendon.(16, 56, 57) Several studies have shown positive correlations between NAPSI scores and ultrasound evidence of enthesopathy.(56, 58)

A recent study comparing nail ultrasound measures in healthy controls to patients with psoriasis or PsA found that the nail plate and nail bed were thickened in patients with psoriasis or PsA, more so in digits with clinical nail symptoms.(59) However, another recent study, which also included patients with rheumatoid arthritis
and osteoarthritis, found that nail plate thickening was also associated with osteoarthritis and concluded that PsA was best discriminated using the power Doppler signal at the nail enthesis. Overall, imaging techniques, including ultrasound and magnetic resonance imaging, can provide valuable data on structural and inflammatory changes to the nail unit and anatomically associated joints. Imaging findings generally correlate well with clinical observations and could potentially be used as part of clinical assessments of NP. Although only one of the NP clinical studies found in our search (Table 2 and Supplementary Table 1) incorporated imaging as a diagnostic or outcome measure, expanded use of imaging should be considered in future research.

Recent Developments in the Treatment of NP

Overview of Available Therapies

In recent years, substantial progress has been made in understanding the pathogenesis of psoriatic skin and joint disease, and several highly effective therapies are now available for the treatment of moderate to severe disease. However, NP research has been far more limited, and determining an appropriate treatment course can be challenging. This leads to the undertreatment of NP, which is a significant unmet need in the management of psoriatic disease; in a Dutch Psoriasis Association survey, only 16% of patients were receiving treatment for NP. (48)

Topical therapies are often used as first-line treatment for mild NP, but efficacy is modest even when disease is limited to minimal dystrophy in 1 or 2 nails. Application of topical therapies to nails is messy, most drugs do not adequately
penetrate the nail bed and nail matrix, and use of topical corticosteroids can result in
nail and underlying phalanx atrophy, nail striae, telangiectasias, tachyphylaxis, and
other adverse consequences associated with systemic absorption of the
corticosteroid. (5, 66)

Available data, generally from cohort studies (Table 2), indicate that intralesional
injection of corticosteroids or methotrexate directly into the nail matrix can be an
effective treatment for NP; however, these procedures are unpopular among patients
and physicians because they can be very painful and time consuming, with side effects
including subungual hematomas, short-term paresthesia, and atrophy at the injection
site. (5, 66, 67)

The traditional oral systemic therapies—cyclosporine, methotrexate, acitretin,
and leflunomide—generally provide modest efficacy; many physicians consider these
agents to be inadequate or inappropriate for the treatment of NP in the absence of
significant skin disease. (5, 64, 66)

There are now several classes of biologic and small-molecule therapies
approved for the treatment of moderate to severe plaque psoriasis and/or PsA,
including targeted inhibitors of tumor necrosis factor (TNF), interleukin (IL)-12/23, IL-
17A, IL-23, phosphodiesterase 4, and Janus kinases. These agents have all
demonstrated significant efficacy in psoriatic skin and/or joint disease, but because they
are not specifically indicated for the treatment of NP, physicians can face insurance
reimbursement challenges in patients with moderate to severe nail disease with minimal
or no skin or joint involvement.
Clinical Trials Evaluating Efficacy in NP

The 1546 articles identified by the literature search for approved systemic drugs included 66 clinical studies that reported outcomes for NP. Nail measures were a primary study outcome in 22 of the included articles, a secondary outcome in 25 articles, and a retrospective or post hoc outcome in the remaining 19. Half of the articles reported data for various patient subgroups, including one with “nail symptoms at baseline,” and half were analyses that reported only data for patients with nail symptoms. Nineteen articles reported prospective studies dedicated to NP (Table 2), the remainder were subgroup analyses (Supplementary Table 1). Moderate or severe psoriasis ± PsA was a clinical trial inclusion criterion in 33 articles, active PsA an inclusion criterion in 9 articles, and psoriasis and/or PsA in 6.

Twenty-two of the included articles reported placebo-controlled trials, including 6 articles reporting trials that also included an active comparator (UNCOVER-3,(68, 69) VOYAGE 1 & 2,(35, 37) and LIBERATE(70)), and 5 articles reported head-to-head trials with no placebo arm. Sixty-one articles reported trials focused on single agents, including nonbiologics, TNF inhibitors, IL-12/23 inhibitors, IL-17A inhibitors, IL-23 inhibitors, and targeted synthetic disease-modifying antirheumatic drugs.

Perhaps the most notable observation about these studies (Table 2 and Supplementary Table 1) is the high level of heterogeneity, highlighting the need for a common clinical measure to allow for comparison across studies. Although many studies used variations of the NAPSI, this index is not standardized and is heterogeneous in its subtypes and application.(71) Some studies have reported raw scores, some have reported percentage reductions from baseline, and others have
reported the proportion of patients meeting percentage reduction thresholds (eg, NAPSI50) modeled on commonly used Psoriasis Area and Severity Index (PASI) targets, such as PASI75 and PASI100 (Table 2). It is important to note that the relatively slow growth of nails versus skin means that results can take longer to manifest, particularly for toenails, which means that trials may need to have longer follow-up to adequately assess nail outcomes.

The reports for nonbiological treatments had the greatest diversity in nail scoring methods. In the studies where NAPSI was reported, nonbiologics improved NAPSI by 40–50% after 4–6 months. In general, the biologic therapies were reported to achieve these levels of NAPSI improvement more rapidly, as early as week 12. Most studies of biologics showed that NAPSI continued to improve, with NAPSI improvements rising to the 70–90% range for some drug types. Given the broad range of therapies used to treat NP, results from active-comparator studies may help inform treatment decisions. Real-world prospective studies have shown that biologic therapies are generally significantly more effective than conventional therapies. (72) Comparative studies of different TNF inhibitors have shown that infliximab provides greater improvement in NP than etanercept or adalimumab; however, treatment with infliximab is associated with higher risk of secondary fungal infection in patients with nail scrapings negative for fungus at baseline. (73-75) Several comparisons between different classes of biologic agents have been undertaken. Treatment with the IL-17A inhibitor ixekizumab provided greater improvement in NP than treatment with the TNF inhibitor etanercept over 12 weeks in the UNCOVER-3 study. (68, 69) Data from the VOYAGE 1(37) and VOYAGE 2(35) trials showed that nail improvements with the IL-23 inhibitor
guselkumab were comparable to those observed with adalimumab through 24 weeks of treatment but f-PGA responses were superior at week 48. These results suggest that targeting the IL-17–IL-23 pathway may be a more effective long-term NP treatment strategy than blocking TNF. The importance of the IL-17 axis was highlighted in the TRANSFIGURE trial (76) (NCT01807520), a placebo-controlled study evaluating secukinumab specifically in patients with NP. Secukinumab led to NAPSI reductions at 16 and 32 weeks that were superior to placebo and similar to, or numerically greater than, those with other biologics at similar time points.

Accurate comparisons of data between studies are made difficult by the heterogeneity of patient populations in subanalyses investigating NP, the fact that less than one-third of articles reported placebo-controlled trials, and the differing nail outcome measures used. This suggests a need for further placebo-controlled, randomized trials focused on NP. However, the rates of nail growth mean that responses to treatment will not be fully captured during typical placebo-controlled periods of ≤24 weeks. For example, in the TRANSFIGURE trial, between week 16 (the endpoint of the placebo-controlled phase) and week 32, nail symptoms continued to improve versus baseline: the mean percentage reduction in fingernail NAPSI was a factor of 1.4 larger at week 32 versus week 16, and that of the target toenail NAPSI a factor of 2.3 larger.(76) (NCT01807520)

**Guidelines for Treatment of NP**

In 2015, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) included NP as 1 of the 6 key domains of PsA (peripheral arthritis, axial...
disease, enthesitis, dactylitis, psoriasis, and nail disease).(77) For treatment of patients with moderate to severe NP, the 2015 GRAPPA treatment guidelines recommended biologic treatment with TNF inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors, choosing therapy to address as many disease domains as possible.

The recently published “Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics(78) recommended biologic monotherapies for treatment of adult patients with moderate to severe plaque psoriasis affecting the nails (TNF inhibitors: adalimumab, etanercept, or infliximab; IL-12/23 inhibitor: ustekinumab; IL-17 inhibitors: secukinumab or ixekizumab).

Conclusions
NP is an important predictor of enthesitis associated with the early stages of PsA—patients with psoriasis are 3 times more likely to develop PsA if they have nail symptoms. The nail sits at a fascinating nexus of the appendicular and musculoskeletal system due to the close relationship of the extensor tendon enthesis to nail structures. NP is 1 of the 6 key domains of PsA that need to be assessed to establish the prognosis and optimal treatment for individual patients.(77, 79) As such, it is important for rheumatologists and dermatologists to accurately diagnose and treat NP to potentially delay the onset and progression of joint disease. However, given that systemic therapies are not specifically indicated for the treatment of NP in the absence of moderate to severe skin or joint disease, there are several unmet needs in daily practice, including the lack of a simple, validated, and widely accepted NP scoring system and well-defined treatment guidelines for patients with NP without moderate or
severe skin symptoms or active PsA. Further randomized studies investigating
treatment of NP are needed to gather a more comprehensive pool of data. Recent
imaging studies have provided important data on the anatomical link between NP and
musculoskeletal manifestations of psoriatic disease. Expanded use of imaging
modalities could be a valuable way to inform NP diagnosis and treatment decisions.

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Table 1: Comparison of Nail Scoring Systems Used in Studies of Currently Approved Treatments for Psoriasis and/or PsA

Table 2: Overview of Dedicated, Prospective Nail Psoriasis Studies of Currently Approved Treatments for Psoriasis and/or PsA
FIGURES

Figure 1. (A) Structural components of the nail unit. (B) The subdivisions of the nail matrix. (C) Pit formation in the nail plate arising from the nail matrix. (D) Anatomical relationship between the nail and distal interphalangeal extensor tendon enthesitis: histology sections showing the superficial lamina (SL) and deep lamina (DL) from the extensor tendon (ET) are associated with the nail root (NR) and matrix.

(A), (B), and (C) reprinted from Jiaravuthisan M, et al. J Am Acad Dermatol. 2007;371(9626):1753-1760, Copyright 2007, Published by Elsevier.


Figure 2. Examples of (A) nail matrix and (B) nail bed psoriasis.

Images courtesy of Phoebe Rich, MD.

Figure 3. Example of division of a nail into quadrants and instructions for grading using the Nail Psoriasis Severity Index.

Figure 4. (A) Ultrasound imaging of the nail/enthesis complex in a 64-year-old woman with psoriasis, psoriatic arthritis, and nail disease. (B) Up arrow: extensor tendon fibers split and fuse with the periosteum over the terminal phalanx, which is connected to the nail bed, thus indirectly anchoring the enthesis to the bone of the phalanx. (C) Down arrow: extensor tendon fibers enveloping the nail root. DP, distal phalanx; MP, middle phalanx.

Images courtesy of Catherine J. Bakewell, MD.
Table 1: Comparison of nail scoring systems used in studies of currently approved treatments for psoriasis and/or PsA

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>NAPSI(38, 39) (by quadrant)</th>
<th>Target NAPSI(38, 39) (by quadrant)</th>
<th>mNAPSI(38, 40) (whole nail)</th>
<th>N-NAIL(34) (whole nail)</th>
<th>f-PGA(80) (all nails)</th>
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<tbody>
<tr>
<td>Beau lines</td>
<td>–</td>
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<td>–</td>
<td>Absent=0; 1 line=1; 2 lines=2; ≥3 lines=3</td>
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<tr>
<td>Leukonychia</td>
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<td>Present=1 per quadrant</td>
<td>Present=1</td>
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<tr>
<td>Nail plate crumbling</td>
<td></td>
<td>Present=1 per quadrant</td>
<td>Absent=0; 1–25%=1; 26–50%=2; &gt;50%=3</td>
<td>Absent=0; mild=1; moderate=2; severe=3</td>
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<tr>
<td>Pitting</td>
<td></td>
<td>Present=1 per quadrant</td>
<td>Absent=0; 1–10 pits=1; 11–49 pits=2; ≥50 pits=3</td>
<td>Absent=0; mild=1; moderate=2; severe=3</td>
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<tr>
<td>Red spots in the lunula</td>
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<td>Present=1 per quadrant</td>
<td>Present=1</td>
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<td>clear=0 minimal=1 mild=2 moderate=3 severe=4</td>
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<td>Hyperkeratosis</td>
<td>Score 1 for each nail quadrant with nail matrix symptoms (0–4)</td>
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<td>Present=1</td>
<td>Absent=0; 1 mm=1; 2 mm=2; ≥3 mm=3</td>
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<tr>
<td>Oil drop or salmon patch</td>
<td></td>
<td>Present=1 per quadrant</td>
<td>Absent=0; 1–10%=1; 11–30%=2; &gt;30%=3</td>
<td>Absent=0; 0–25%=1; 25–50%=2; &gt;50%=3</td>
<td></td>
</tr>
<tr>
<td>Onycholysis</td>
<td></td>
<td>Present=1 per quadrant</td>
<td>Present=1</td>
<td></td>
<td></td>
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<tr>
<td>Splinter hemorrhages</td>
<td></td>
<td>Present=1 per quadrant</td>
<td>Present=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score range per nail (or “target” nail)</td>
<td>0–8</td>
<td>0–32</td>
<td>0–13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0–15</td>
<td>0–4</td>
</tr>
<tr>
<td>Total for fingernails</td>
<td>0–80</td>
<td>–</td>
<td>0–130&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0–150</td>
<td>0–4</td>
</tr>
<tr>
<td>Total for all nails</td>
<td>0–160</td>
<td>–</td>
<td>0–130&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0–150</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: f-PGA, Fingernail Physician’s Global Assessment; mNAPSI, modified NAPSI; NAPSI, Nail Psoriasis Severity Index; N-NAIL, Nijmegen-Nail Psoriasis Activity Index Tool.

<sup>a</sup>Note that the mNAPSI is sometimes listed as 0–14 per nail, 0–140 total, due to a misprint in the original paper.
Table 2: Overview of dedicated, prospective nail psoriasis studies of currently approved treatments for psoriasis and/or PsA

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Article (study)</th>
<th>Patient population</th>
<th>Nail PsO outcome measure(s)</th>
<th>Key nail PsO efficacy results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonbiologics</strong></td>
<td></td>
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<tr>
<td><strong>Acitretin</strong></td>
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<tr>
<td>Acitretin (0.2 to 0.3 mg/kg QD for 6 months)</td>
<td>Tosti 2009(81)</td>
<td>M/S isolated fingernail PsO (n=36)</td>
<td>Primary: NAPSI (0–80), target mNAPSI (0–13)</td>
<td>Change from BL to 6 months, mean %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NAPSI</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Modified target NAPSI</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
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<tr>
<td>Cyclosporine (3.5 mg/kg/day) ± topical calcipotriol BID</td>
<td>Feliciani 2004(82)</td>
<td>S PsO with nail PsO (n=54)</td>
<td>Primary: 3-level improvement score (+, ++, ++++)</td>
<td>Patients with improved clinical appearance of nails, %</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYC + topical</td>
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<td></td>
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<td></td>
<td>Month 3</td>
</tr>
<tr>
<td>Cyclosporine (3 mg/kg BID)</td>
<td>Abe 2011(83)</td>
<td>Pretreated for nail PsO (n=32)</td>
<td>Primary &quot;Nail PASI&quot; (unclear)</td>
<td>Complete resolution in 25% Significant improvement in 50%</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td></td>
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<tr>
<td>Methotrexate (15 mg QW, initial dose) vs cyclosporine (5 mg/kg QD)</td>
<td>Gumusel 2010(84)</td>
<td>PsO or PsA and nail PsO (n=37)</td>
<td>Primary: NAPSI (0–80)</td>
<td>NAPSI change from BL, mean %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 weeks: MTX (−43.3), CYC (−37.2)</td>
</tr>
<tr>
<td>Methotrexate (15 mg to 25 mg QW)</td>
<td>Krajewska-Wlodarcyzk 2018(63)</td>
<td>Nail PsO, DIP enthesitis, MTX naive (n=319 nails in 32 patients)</td>
<td>Primary: US imaging of nail plate, nail bed and nail matrix Secondary: mNAPSI (0–130)</td>
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<td>Nail plate</td>
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<td>PsO pts</td>
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<td>Nail bed</td>
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<td>PsO pts</td>
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<td>Nail matrix</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>PsO pts</td>
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<tr>
<td><strong>Triamcinolone</strong></td>
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<tr>
<td>Triamcinolone acetonide injection (10 mg/ml) into nail bed/matrix (4 sites, repeated at 2 months if poor response)</td>
<td>Saleem 2008(85)</td>
<td>Nail PsO (n=35, 100 nails)</td>
<td>Primary: 0 to 3 severity score for various nail pathologies</td>
<td>Response at 6 months (number of nails)</td>
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<tr>
<td></td>
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<td></td>
<td>Nail plate</td>
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<td></td>
<td>Partial</td>
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<td></td>
<td></td>
<td>Complete</td>
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<td></td>
<td>Onycholysis</td>
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<td></td>
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<td></td>
<td></td>
<td>Subungual Hyperkeratosis</td>
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<td></td>
<td>Ridging</td>
</tr>
<tr>
<td>Treatment</td>
<td>Study Details</td>
<td>Primary:</td>
<td>Target NAPSI, mean reduction from BL (%)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------</td>
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<tr>
<td>Triamcinolone acetonide (intra-matricial needle-free injection)</td>
<td>Nantel-Battista 2014(86)</td>
<td>Nail PsO (n=17)</td>
<td>46.25%</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone (intralesional injection)</td>
<td>Boontaveeyuw at 2018(87)</td>
<td>Nail PsO (n=48 nails)</td>
<td>Temporary reduction in target NAPSI over 1–4 months</td>
<td></td>
</tr>
<tr>
<td>Intramatrical injection of: Triamcinolone acetonide (10 mg/ml) vs methotrexate (25 mg/ml) vs cyclosporine (50 mg/ml)</td>
<td>Mittal 2018(67)</td>
<td>17 patients with 90 affected fingernails</td>
<td>Temporary reduction in target NAPSI over 1–4 months</td>
<td></td>
</tr>
<tr>
<td><strong>Biologics</strong></td>
<td></td>
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<tr>
<td><strong>TNF inhibitors: adalimumab</strong></td>
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<tr>
<td>Adalimumab (80 mg at week 0, then 40 mg Q2W)</td>
<td>Rigopoulos 2010(88)</td>
<td>Primary: NAPSI fingers (0–80), NAPSI toes (0–80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (real-world use)</td>
<td>Khobzey 2017(89)</td>
<td>NAPSI change from BL, mean %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (40 mg Q2W) vs PBO</td>
<td>Eilewski 2018(80)</td>
<td>Primary: mNAPSI (0–130), target mNAPSI (0–13) Secondary: mNAPSI75, mean %</td>
<td></td>
<td></td>
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<tr>
<td><strong>TNF inhibitors: etanercept</strong></td>
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<tr>
<td>Etanercept (50 mg BIW for 12 weeks then QW for 12 weeks; or QW 24 weeks)</td>
<td>Ortonne 2013(90)</td>
<td>Primary: Target NAPSI (excluding thumb, 0–8) Secondary: Target NAPSI change from BL, mean</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table: Biologics

#### TNF inhibitors: adalimumab

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Primary:</th>
<th>NAPSI, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (80 mg at week 0, then 40 mg Q2W)</td>
<td>NAPSI fingers (0–80), NAPSI toes (0–80)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab (real-world use)</td>
<td>NAPSI change from BL, mean %</td>
<td></td>
</tr>
<tr>
<td>Adalimumab (40 mg Q2W) vs PBO</td>
<td>mNAPSI75, mean %</td>
<td></td>
</tr>
</tbody>
</table>

#### TNF inhibitors: etanercept

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Primary:</th>
<th>NAPSI change from BL, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (50 mg BIW for 12 weeks then QW for 12 weeks; or QW 24 weeks)</td>
<td>Target NAPSI change from BL, mean</td>
<td></td>
</tr>
</tbody>
</table>

### Table: Targets NAPSI

<table>
<thead>
<tr>
<th>Week 24</th>
<th>QW</th>
<th>BIW/QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.6%</td>
<td>3.4%</td>
<td>P&lt;.001</td>
</tr>
<tr>
<td>Biologics</td>
<td>Treatment</td>
<td>Design</td>
</tr>
<tr>
<td>----------</td>
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</tr>
<tr>
<td><strong>TNF inhibitors: infliximab</strong></td>
<td>Infliximab (5 mg/kg IV at 0, 2, 6, 14, and 22 weeks)</td>
<td>Bianchi 2005(91)</td>
</tr>
<tr>
<td></td>
<td>Infliximab (infusion of 5 mg/kg at weeks 0, 2, and 6, then Q8W)</td>
<td>Rigopoulos 2008(92)</td>
</tr>
<tr>
<td><strong>IL-12/23 inhibitor: ustekinumab</strong></td>
<td>Ustekinumab (45 mg at weeks 0 and 4, then Q12W)</td>
<td>Patsatsi 2011(93)</td>
</tr>
<tr>
<td></td>
<td>Ustekinumab (45 mg/90 mg [for BW under/over 100 kg] at weeks 0 and 4, then Q12W)</td>
<td>Rigopoulos 2011(94)</td>
</tr>
<tr>
<td><strong>IL-17A inhibitors: secukinumab</strong></td>
<td>Secukinumab (300 mg or 150 mg Q4W) vs PBO</td>
<td>Reich 2018(76) (NCT01807520) (TRANSFIGURE)</td>
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<tr>
<td><strong>Head-to-head studies</strong></td>
<td>Adalimumab (80 mg at week 0, 40 mg at week 1, then Q2W) vs etanercept (50 mg BIW for 12 weeks then 25 mg BIW for 12 weeks) vs infliximab (infusion of 5 mg/kg at weeks 0, 2, and 6, then Q8W)</td>
<td>Saraceno 2013(75)</td>
</tr>
</tbody>
</table>
Abbreviations: ADA, adalimumab; APL, apremilast; BIW, twice a week; BL, baseline; B-SNIPI50, 50% improvement in Brigham Scalp Nail Inverse Palmoplantar Psoriasis Index; CYC, cyclosporine; CZP, certolizumab pegol; DMARD, disease-modifying antirheumatic drugs; ETN, etanercept; f-PGA, Fingernail Physician’s Global Assessment; GOL, golimumab; GUS, guselkumab; IFX, infliximab; IQR, inter-quartile range; JAK, Janus kinase; MTX, methotrexate; mNAPSI; modified NAPSI; M/S, moderate to severe; NAPPA, Nail Assessment in Psoriasis and Psoriatic Arthritis; NAPSI, Nail Psoriasis Severity Index; NAPSI50/75/100, 50/75/100% reduction from BL in NAPSI; N-NAIL, Nijmegen-Nail Psoriasis Activity Index Tool; NPPFS, Nail Psoriasis Physical Functioning Severity; n.s., not significant; PBO, placebo; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; PsO, psoriasis; pts, patients; RWD, real-world data; S, severe; SEC, secukinumab; TOF, tofacitinib; TRI, triamcinolone; UST, ustekinumab; VAS, visual analog scale.
Figure 1. (A) Structural components of the nail unit. (B) The subdivisions of the nail matrix. (C) Pit formation in the nail plate arising from the nail matrix. (D) Anatomical relationship between the nail and distal interphalangeal extensor tendon enthesitis: histology sections showing the superficial lamina (SL) and deep lamina (DL) from the extensor tendon (ET) are associated with the nail root (NR) and matrix. (A), (B), and (C) reprinted from Jiavavutthisan M, et al. J Am Acad Dermatol. 2007;371(9626):1753-1760, Copyright 2007, Published by Elsevier. (D) reproduced from McGonagle D. J Eur Acad Dermatol Venereol. 2009;23(Suppl. 1):9-13. © 2009 The Author. Journal compilation © 2009 European Academy of Dermatology and Venereology. Adapted from: Tan AL et al. Rheumatology. 2007;46(2):253-256 by permission of Oxford University Press.

206x482mm (150 x 150 DPI)
Figure 2. Examples of (A) nail matrix and (B) nail bed psoriasis. Images courtesy of Phoebe Rich, MD.
Figure 4. (A) Ultrasound imaging of the nail/enthesis complex in a 64-year-old woman with psoriasis, psoriatic arthritis, and nail disease. (B) Up arrow: extensor tendon fibers split and fuse with the periosteum over the terminal phalanx, which is connected to the nail bed, thus indirectly anchoring the enthesis to the bone of the phalanx. (C) Down arrow: extensor tendon fibers enveloping the nail root. DP, distal phalanx; MP, middle phalanx. Images courtesy of Catherine J. Bakewell, MD.