

Nail Psoriasis: An Updated Review of Currently Available Systemic Treatments

Teresa Battista, Massimiliano Scalvenzi*, Fabrizio Martora^{ID}*, Luca Potestio^{ID}, Matteo Megna

Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

*These authors contributed equally to this work

Correspondence: Fabrizio Martora, Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, Napoli, 80131, Italy, Tel +39 - 81 - 7462457, Fax +39 - 81 - 7462442, Email fabriziomartora92@libero.it

Background: Nail psoriasis (NP) has a prevalence that ranges from 10 to 82% among patients with psoriasis (PsO) and is one of the most common difficult to treat site of psoriasis. We performed a thorough review of the literature, exploring evidence regarding all available NP systemic treatments, describing also in detail NP dedicated clinical trials.

Methods: A literature search was conducted in PubMed and Embase prior to February 2023 using a combination of the terms “nail” AND “psoriasis” AND “systemic therapy” AND/OR “systemic treatment”. A total of 47 original studies and case reports were reviewed in this article.

Results: Systemic therapies should be considered when the disorder involves more than 3 nails, has extensive skin and joint involvement, and has a significant impact on QoL, due to their best long-term efficacy. In detail, conventional and biologic systemic drugs demonstrated efficacy in recent trials, including acitretin, methotrexate, cyclosporine, apremilast, adalimumab, infliximab, etanercept, certolizumab, golimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab and tildrakizumab.

Conclusion: Several therapies have demonstrated efficacy and safety in the treatment of NP; however, the choice of treatment depends not only on the severity of the nail involvement, but also on whether PsA is present, the patient’s comorbidities other than PsA, previous treatment history, and the patient’s drug preferences.

Keywords: nail psoriasis, psoriasis, treatment, biologics

Introduction

Nail psoriasis (NP) has a prevalence that ranges from 10 to 82% among patients with psoriasis (PsO) and is one of the most common difficult to treat site of psoriasis.¹ In 5–10% of cases, NP manifests in the absence of cutaneous symptoms.² NP can be associated with pain, cosmetic concerns, and impaired finger function that can significantly impact the patient’s quality of life (QoL).^{3,4} Studies have reported that psoriasis patients with nail involvement have reduced compared to psoriasis patients without nail involvement.⁵ NP presents a heterogeneous clinical spectrum, depending on the part of the affected nail structure, which can be divided into nail matrix (pitting, leukonychia, red spots in the lunula, nail plate crumbling, onychomadesis and Beau lines) or nail bed (salmon patches, onycholysis, nail bed hyperkeratosis, and splinter hemorrhage) alterations.^{6,7} Moreover, the nail structure presents therapeutic challenges, such as poor penetration of topical treatments across the nail plate and pain associated with the use of intralesional therapies.^{7,8} NP is also an independent prognostic factor for comorbidities such as psoriatic arthritis (PsA) and greater degrees of skin severity in plaque psoriasis.⁹ Nails are strongly anchored to the musculoskeletal system and are therefore functionally linked to it. It is believed that given the link between the extensor tendon and the nail matrix, inflammation of this structure may play a key role in nail pitting in both PsA and psoriasis, supporting a strong significant higher risk of PsA in NP subjects.¹⁰ There are several different scoring systems for NP severity, including the Nail Psoriasis Severity Index (NAPSI), mNAPSI (Modified Nail Psoriasis Severity Index), and PNSS (Psoriasis Nail Severity Score).¹¹ NP is

one of the most challenging areas to treat for the factors above explored, and it deserves a prompt treatment due to increased PsA risk as well as limitations in patients' everyday life. Topical and injectable therapies are recommended for NP with few nails involved. Systemic therapies, including biologics, can be considered for patients with multiple and resistant nail disease, impaired QoL, and severe skin and joint involvement.⁷ 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 studies have been more limited, possibly leading to the undertreatment of NP, which is a significant unmet need in the management of psoriatic disease.¹² Indeed, in a Dutch Psoriasis Association survey, only 16% of patients were receiving treatment for NP.¹¹ Herein, we performed a thorough review of the literature, exploring evidence regarding all available NP systemic treatments, describing also in detail NP dedicated clinical trials.

Methods

A literature search was conducted in PubMed and Embase prior to February 2023 using a combination of the terms “nail” AND “psoriasis” AND “systemic therapy” AND/OR “systemic treatment”. Only studies written in the English language were reviewed. All original prospective, retrospective studies, nonexperimental descriptive studies and case reports of systemic therapies for NP were chosen for the purpose of this review. A total of 47 original studies and case reports were reviewed in this article. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. The following information was extracted from each study: author, year of publication, design of study, patient type, details of the interventions, baseline nail psoriasis involvement, and the improvement at each visit till the end of study. We have made [Tables 1^{13–53}](#) and [2^{54–113}](#) to collect most of the studies we have cited in the text, more information can be found in the two tables.

Results

NP Treatment: Introduction

NP clinical manifestations depend on which part of the nail is involved.^{123,124} Treatment of nail disease can be divided into involvement of the nail matrix, nail bed or those with widespread nail involvement.^{123,124} In nail-bed psoriasis, the topical agent should be able to penetrate to the psoriatic inflammation of the nail bed and therefore cutting the onycholytic part of the nail plate should be encouraged before medication is applied.⁷ In the case of matrix involvement only, intralesional steroid injections are considered the treatment of choice.¹²⁵ For those presenting with psoriasis of the nail bed, first-line treatment can include any of the following: topical keratolytic agents, topical steroids with or without vitamin D analogues, topical retinoids, tacrolimus 0.1% ointment or intralesional steroids.¹²⁵ Topical therapy represents one of the oldest and most well-studied treatment methods for nail psoriasis. Multiple medications have been studied, including calcipotriol ointment,¹²⁶ anthralin therapy,¹²⁷ 5-fluorouracil,¹²⁸ tazarotene,¹²⁹ cyclosporin,¹³⁰ vitamin D analogue/corticosteroid formulations,¹³¹ and tacalcitol.¹³² Local injection therapies include steroid injections¹³³ and methotrexate injections.^{134–137} The optimal pharmaceutical formulation of topical therapy is that of an ointment or solution.¹³¹ Achieving optimal therapeutic concentrations of topical medications is challenging with nail psoriasis given the presence of the nail plate, which can serve as an impermeable physical barrier.⁷ Therefore, identifying the exact anatomical location of psoriatic nail disease is key to determining how and where topical medications should be applied. While local therapies are preferred when fewer than three nails are involved, systemic therapies, including biologics, may be considered for patients with multiple and resistant nail disease, impaired quality of life, and severe skin and joint involvement.¹²⁵

Acitretin

Acitretin is the active metabolite of etretinate, and it is the most widely used systemic retinoid in the management of psoriasis.¹³

Brazelli et al report the optimal results with acitretin in a patient with psoriasis limited to the nails. All his fingernails and two toenails were affected, being resistant to topical corticosteroid and calcipotriol. A treatment with 0.5 mg/kg

Table 1 Studies Evaluating Effectiveness of Conventional Systemic Drugs in Nail Psoriasis

Drug	Author	Study Design	Participants	Dosage	Study Period	Efficacy
Acitretin	Brazzelli et al, 2004 ¹⁴	Case report	1	0.5 mg/kg per day	6 months	NA
Acitretin	Brazzelli et al, 2009 ¹⁵	Case report	1	25mg/day	2 months	NA
Acitretin	Tosti et al, 2009 ¹⁶	Real-life retrospective study	36	0.2 or 0.3 mg/kg per day	6 months	Mean NAPS I score reduced by 41% after 6 months
Acitretin	Ricceri et al, 2013 ¹⁷	Case report	1	25 mg/day in association to 5% urea nail lacquer	5 months	NA
Acitretin	Krajewska-Włodarczyk et al, 2021 ¹⁸	Real-life Prospective study	41	0.6 to 0.8 mg/kg per day	6 months	Reduced thickness of the nail plate
Acitretin	Graceffa et al, 2020 ¹⁹	Case report	1	0.3mg/kg	14 months	NAPS I score reduced from 45 to 9 after 14 months of therapy
Acitretin	Mukai et al, 2012 ²⁰	Real-life prospective study	20	0.3 mg/kg/day for 30 days, later raised to 0.5 mg/kg/day	4 months	Mean NAPS I score worsened from 20 to 20.5. Three patients improved 50% of the initial NAPS I and 1 had an improvement of 75%
Methotrexate	Gümüşel et al, 2011 ²²	One blind randomized study	Thirty-seven psoriatic patients with nail involvement were randomized to treatment with methotrexate (initial dose, 15 mg per week) or cyclosporine (initial dose, 5 mg per kg of bodyweight per day) for 24 weeks	15 mg of methotrexate administered weekly 5mg/kg daily of cyclosporine reduced after 3 months to 2.5–3.5 mg/kg daily	6 months	The mean percentage reduction in NAPS I for MTX and cyclosporine was 43.3 and 37.2%, respectively
Methotrexate	Tsiskarishvili et al, 2011 ²³	Real-life retrospective study	39	25 mg weekly	6 months	Mean NAPS I score reduced by 75% at 24 weeks

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Table 1 (Continued).

Drug	Author	Study Design	Participants	Dosage	Study Period	Efficacy
Methotrexate	Coates et al, 2016 ²⁵	Randomized controlled trial	117	15 mg/week for 4 weeks, 20 mg/week for 2 weeks, and 25 mg/week thereafter if tolerated	3 months	At 12 weeks, the median change in modified mNAPSI score was -2 (interquartile range -8 to 0), the median change in the nail plate score was 0 (interquartile range -3.75 to 1), and the median change in the nail bed score was -1 (interquartile range -4.75, 0)
Methotrexate	Warren et al 2017 ²⁷	Multicentre randomised double-blind Placebo-controlled Phase 3 trial	851	The patients received other MTX at a starting dose of 17.5 mg/week or placebo for the first 16 weeks, followed by methotrexate treatment of all patients up to 52 weeks	52 weeks	At baseline mean NAPSI score was 4 (range 1–8). At 16 weeks, the MTX group had a reduced NAPSI score, compared with no change in the placebo group. At 52 weeks, complete clearance of nail disease was seen in 14% of patients with active NP at baseline
Methotrexate	Drach et al, 2019 ²⁸	Real-life retrospective study	66	NA	12 weeks	Nail psoriasis improved from a mean NAPSI of 16.4 to 13.0 after 12 weeks
Methotrexate	Lee et al, 2009 ²⁹	Case report	1	5 mg per week	13 months	Complete resolution of the severe nail psoriasis was achieved after 9 and 13 months of methotrexate therapy for fingers and toes, respectively
Cyclosporine	Karanikolas et al, 2011 ³²	Prospective non randomized unblinded clinical trial	57, 58, and 55 patients who received cyclosporine (2.5–3.75 mg/kg/day), adalimumab (40 mg every other week), or combination	2.5–3.75 mg/kg/day	12 months	A total of 44% of patients treated with cyclosporine, 56% of patients treated with adalimumab, and 100% treated with a combination of both achieved reduction of 50% in NAPSI score (NAPSI50)

Dimethylfumarate	Augustin et al 2022 ³⁵	Interim analysis of the prospective, noninterventional SKILL study	676 patients	120 mg twice daily	52 weeks	The mean nail-Physician Global Assessment (nail-PGA) of patients with nail disease at baseline (nail-PGA > 0) improved from 1.8 at baseline to 0.6 (at week 52. Of the patients presenting with nail involvement at baseline, 50.6% were clear (nail-PGA of 0) at week 52, and 70.2% of patients experienced an improvement of their nail involvement until week 52.
Dimethylfumarate	Vlachou et al, 2007 ³⁶	Case report	1	120 mg twice daily	5 months	Onycholysis improvement
Photochemotherapy	Marx et al, 1980 ³⁷	1980	10	0.6 mg/kg 2–3 times a week	NA	Nail psoriasis improved in 70% of patients

Table 2 Studies Evaluating Effectiveness of Small Molecules and Biologic in Nail Psoriasis

Drug	Author	Study Design	Participants	Dosage	Study Period	Efficacy
Apremilast	Rich et al, 2016 ⁴⁰	Phase III trial	824	Apremilast 30 mg twice daily or placebo	32 weeks	The mean percentage reduction from baseline in target nail NAPS I score for these patients, who either received apremilast 30 mg initially or were re-randomized from placebo to apremilast at week 32 ranged from 60 to 64%.
Apremilast	Reich et al, 2018 ⁴¹	Phase III trial	250	Placebo, apremilast 30 mg twice daily or etanercept 50 mg weekly through Week 16; thereafter, all patients continued or switched to apremilast through Week 104	104 weeks	At Week 104, NAPS I mean change from baseline was -48.1% to -51.
Etanercept	Ortonne et al, 2013 ⁴⁵	Phase III trial	72	50 mg twice weekly for 12 weeks followed by once weekly, or 50mg once weekly for 24 weeks	24 weeks	At week 24, mean NAPS I showed a reduction in both etanercept groups. BIW/QW group: - 4.3; QW/QW group: - 4.4
Etanercept	Rallis et al, 2008 ⁴⁸	Case report	1	50 mg etanercept weekly	6 weeks	Complete resolution
Infliximab	Bianchi et al, 2005 ⁵⁴	Open label Prospective study	25	5mg/kg at weeks 0,2,6 and every 8 weeks	22 weeks	All patients showed a 50% reduction of the initial mNAPS I.
Infliximab	Fabroni et al, 2011 ⁵⁵	Real-life retrospective study	48	5 mg/kg	38 weeks	The mean NAPS I $\pm$ SD got down to 18.58 ± 9.42 at week 14, to 9.54 ± 4.71 at week 22 and further down to 7.21 ± 4.92
Infliximab	Reich et al, 2005 ⁵⁷	Phase III trial	378	5mg/kg	46 weeks	The percentage improvement from baseline of the NAPS I was significantly greater in infliximab-treated patients than in placebo-treated patients at weeks 10 (26.0 ± 42.3 vs -5.9 ± 54.3 ; $p < 0.0001$) and 24 (56.3 ± 43.4 vs -3.2 ± 62.3 ; $p < 0.0001$).

Adalimumab	Rigopoulos et al, 2010 ⁶⁴	Phase III trial	21	Adalimumab at a dose of 80 mg at baseline, 40 mg at week 1, and 40 mg every 2 weeks thereafter	24 weeks	In patients with only cutaneous lesions, mean NAPS I score decreased from 10.57 ± 1.21 for the fingernails and 14.57 ± 2.50 for the toenails at baseline to 5.57 ± 0.78 and 9.57 ± 2.17 at week 12, and to 1.57 ± 0.20 and 4.14 ± 1.58 at week 24, respectively. In patients with PsA, mean NAPS I score decreased from 23.86 ± 2.00 for the fingernails and 29.29 ± 2.87 for the toenails at baseline to 12.86 ± 1.05 and 19.21 ± 2.07 at week 12, and to 3.23 ± 0.32 and 10.00 ± 1.40 at week 24, respectively ⁶⁴
Adalimumab	Sola-Ortigosa et al, 2012 ⁶⁵	Real-life retrospective study	15	80 mg loading dose and thereafter 40 mg every other week	24 weeks	NAPS I score decreased from an initial value of 18.9 ± 12.2 to 8.2 ± 4.7 at week 24
Adalimumab	Elewski et al, 2019 ⁶⁹	Phase III trial	109	80 mg loading dose and thereafter 40 mg every other week	52 weeks	54.4% achieved NAPS I75 at week 52
Adalimumab	Kokolakis et al, 2020 ⁷¹	Real-life multicentre prospective study	267	80 mg loading dose and thereafter 40 mg every other week	24 months	Approximately 42% and 60% of patients achieved NAPS I90 after 12 and 24 months, respectively.
Certolizumab	Mease et al, 2014 ⁷⁵	Phase III trial	409	400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks in one group and every 4 weeks in the other group	24 weeks	mNAPS I change from baseline was -1.6 for the group treated with certolizumab pegol every 2 weeks and -2.0 for the group treated with certolizumab pegol every 4 weeks compared with -1.1 for the placebo group
Certolizumab	Mazzeo et al, 2019 ⁷⁶	Real-life prospective study	8	400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks	52 weeks	NAPS I improved from 50.34 (baseline) to 20.5 (W24) with a further reduction to 10 (W52).

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Table 2 (Continued).

Drug	Author	Study Design	Participants	Dosage	Study Period	Efficacy
Certolizumab	Dattoli et al, 2020 ⁷⁷	Real-life retrospective study	56	400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks	52 weeks	Baseline mNAPSI score was 14.64, with changes from baseline of -5.69 at week 12, -8.77 at week 24 and -12.92 at week 52.
Golimumab	Mease et al, 2020 ⁸⁰	Randomized placebo-controlled trial	480	Patients received either intravenous (IV) golimumab 2 mg/kg at week 0, 4, and then every 8 weeks through week 52, or placebo with crossover at week 24	52 weeks	The mean improvement from baseline in mNAPSI score was significantly greater in patients treated with golimumab versus those treated with placebo at week 14 (-9.6 vs -1.9, $p < 0.0001$) and week 24 (-11.4 vs -3.7, $p < 0.0001$). At week 52, mNAPSI response was maintained in patients randomized to receive golimumab (-11.4 at week 24 and -12.1 at week 52) and increased numerically (from -3.7 to -12.9) in patients who crossed over from placebo to golimumab at week 24
Golimumab	Kavanaugh et al, 2009 ⁸¹	Randomized placebo-controlled trial	405	Label dosage	24 weeks	The median improvement in NAPSI score from baseline to weeks 14 and 24 was significantly greater ($p < 0.001$) in the golimumab 50 mg group (25, 43%) and the golimumab 50 mg group (33, 54%) compared to that in the placebo group (0, 0%, respectively)
Ustekinumab	Rigopoulos et al, 2011 ⁸⁶	Open-label prospective study	27	Label dosage	40 weeks	NAPSI score was assessed at baseline and at weeks 4, 16, 28, and 40. The mean NAPSI score was significantly ($p < 0.001$) decreased from 19.59 ± 7.92 at baseline to 16.96 ± 6.99 at week 4, 9.70 ± 4.47 at week 16, 3.85 ± 3.03 at week 28, and 2.00 ± 2.33 at week 40.

Ustekinumab	Patsasi et al, 2013 ⁸⁷	Open label non randomized study	27	Label dosage	40 weeks	NAPSI median score was significantly ($p < 0.0001$) decreased from 73.0 (range: 12.0–151.0) at baseline to 37.0 (range: 7.0–92.0) at week 16, to 9.0 (range: 0.0–32.0) at week 28 and to 0.0 (range: 0.0–12.0) at week 40.
Ustekinumab	Igarashi et al, 2012 ⁸⁸	Double blind placebo-controlled study	158	Patients were randomized to receive ustekinumab 45 mg ($n = 64$) or 90 mg ($n = 62$) at weeks 0, 4, and every 12 weeks, or placebo ($n = 32$) with cross-over to ustekinumab at week 12	64 weeks	At week 64, the mean percent improvement in target NAPSI was 56.6 ± 43.2 and 67.8 ± 37.5 for the ustekinumab 45 and 90 mg groups, respectively
Ustekinumab	Youn et al, 2017 ⁸⁹	Post hoc analysis of a Phase IV, multicenter, open-label, real-world observational clinical trial, the MARCOPOLO study	81	Label dosage	52 weeks	At week 52, PASI75 and PASI90 were achieved in 70.6% and 39.2%, and these proportions corresponded to 42% and 71% NAPSI improvement rates, respectively.
Ixekizumab	Leonardi et al, 2020 ¹⁰¹	Phase III trial	847 (UNCOVER-1) 751 (UNCOVER-2)	The UNCOVER-1 study compared ixekizumab (80mg Q2W, 80mg Q4W) to placebo in 847 patients. The UNCOVER-2 study compared the same two doses of ixekizumab with etanercept (50 mg twice a week) and placebo in 751 patients	12 weeks	The mean improvements in the NAPSI were 7.24, 7.19, and -2.17 points, respectively ($p < 0.001$) at week 12. Treatment with ixekizumab 80 mg Q2W or Q4W resulted in an equivalent reduction in the NAPSI score (8.6 and 7.39, respectively), which was significantly better than that of patients treated with etanercept (5.34 points) and placebo (0.82 points, $p < 0.001$).

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Table 2 (Continued).

Drug	Author	Study Design	Participants	Dosage	Study Period	Efficacy
Ixekizumab	Van de Kerkhof et al, 2017 ¹⁰²	Post-hoc analysis of UNCOVER-3 study	809	160mg followed by either one injection every 4weeks (Q4W) or every 2 weeks (Q2W).	12 weeks	Ixekizumab demonstrated significant improvement in NAPSI score at week 2 vs etanercept (5.1 vs -7.9%, $p = 0.024$). At week 12, higher NAPSI improvements were reached in the ixekizumab versus placebo groups and in the ixekizumab versus etanercept groups in both the Q4W group [36.7 vs - 34.3% (vs placebo), $p < 0.001$; 36.7 vs 20% (vs etanercept), $p = 0.0048$] and Q2W group [35.2 vs - 34.3% (vs placebo), $p < 0.001$; 36.7 vs 20% (vs etanercept), $p = 0.072$]
Ixekizumab	Elewski et al, 2022 ¹⁰⁶	IXORA-R, IXORA-S, UNCOVER-2, UNCOVER-3, and SPIRIT-H2H trials	NA	NA	NA	Ixekizumab achieved significantly greater simultaneous skin and nail complete clearance than etanercept (UNCOVER-2: $p < 0.001$ and UNCOVER-3: $p < 0.001$) at week 12. Ixekizumab achieved numerically greater simultaneous complete clearance than guselkumab at week 24 ($p = 0.079$), but statistically significant greater simultaneous clearance compared to ustekinumab ($p < 0.001$) and adalimumab ($p = 0.006$) at week 24 and week 52 ($p < 0.001$ and $p = 0.007$, respectively).
Secukinumab	Pistone et al, 2018 ¹⁰⁹	Case series	15	Label dosage	12 weeks	At week 12, NAPSI reduction was by 80%.
Secukinumab	Reich et al, 2019 ¹¹⁰	Phase III trial	198	150 mg or 300 mg weekly for 5 weeks and then every 4 weeks	2.5 years	Both dosages of secukinumab demonstrated superiority over placebo at week 16 [37.9 and 45.3 vs 10.8 (placebo); <0.001], with efficacy maintained at week 32 (52.6 and 63.6, respectively) and at 2.5 years (63.6 and 73.3, respectively).

Brodalumab	Gregoriou et al, 2021 ¹¹⁴	Open-label unblinded study	30	Label dosage	12 weeks	At baseline mean NAPS I score was 44.5. At week 12 mean NAPS I score of fingernails was 9.6 and at week 24 was 2.63; meanwhile at week 12 mean NAPS I score of toenails was 16.1 and at week 24 was 7.2
Bimekizumab	Merola et al, 2023 ¹¹⁵	Phase III trial	556	Label dosage	16 weeks	Among patients with mNAPS I greater than 0 at baseline, at week 16 mNAPS I 0 was achieved by 46% of patients treated with bimekizumab versus 14% of patients taking placebo.
Guselkumab	Ohtsuki et al, 2018 ¹¹⁶	Phase III trial	126	Guselkumab 50 mg or 100 mg at weeks 0, 4 and every 8 weeks, or placebo with cross-over to guselkumab 50 mg or 100 mg at week 16	52 weeks	A significant decrease in mNAPS I score (0–8) of –1.2 and –1.5 was observed for the guselkumab 50 and 100 mg groups, compared with –0.2 for the placebo group, at week 16; improvement was maintained to week 52
Guselkumab	Gerdes et al, 2022 ¹¹⁷	Real-life prospective study	297	Label dosage	52 weeks	Mean NAPS I score was 4.2 at baseline and decreased to 1.2 at W52, with a percentage mean change of –71.4%. Similarly, the mean number of affected nails was 6.8 at baseline, which decreased to 3.3 at W28 and to 2.3 at W52
Risankizumab	Kristensen et al, 2022 ¹¹⁸	Phase III trial	964	Risankizumab 150 mg or placebo at weeks 0, 4 and 16	24 weeks	At baseline mean mNAPS I was 18.1 and mean F-PGA was 2.1. At week 24 mean mNAPS I decreased to 9.8 meanwhile mean PGA-F became 0.8.

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Table 2 (Continued).

Drug	Author	Study Design	Participants	Dosage	Study Period	Efficacy
Risankizumab	Megna et al, 2022 ¹¹⁹	Real-life retrospective study	9	Label dosage	52 weeks	At baseline mean NAPSI (SD) was 9.3 ± 4.7. NAPSI clinical improvement was already assessed at week 4 (6.7 ± 4.6), being statistically significant for the first time at week 16 (4.1 ± 2.4, p < 0.01) and then up to week 52 (1.4 ± 0.8, p < 0.0001).
Tildrakizumab	Ismail et al, 2020 ¹²⁰	Case report	1	Label dosage	NA	Nail psoriasis resolution
Tildrakizumab	Galluzzo et al, 2022 ¹²¹	Real-life retrospective study	18	Label dosage	28 weeks	The NAPSI score decreased by 29.3% at week 12 (from 48.4 to 34.2) and by 67.6% at week 28 (from 48.4 to 15.7)
Tildrakizumab	Brunasso et al, 2022 ¹²²	Real-life retrospective study	8	Label dosage	20 weeks	At week 4, the mean PASI was 6.6 (49% improvement), and the mean mNAPSI was 30.8 (40.6% improvement). At week 20, the mean PASI was 2.1 (84% improvement), and the mean mNAPSI was 5.1 (90% improvement).

per day of oral acitretin was started and continued for 6 months. The clinical improvement of the nails was progressive and with stable results at 6-month follow-up. No systemic side-effects were observed except for cheilitis and palmo-plantar scaling.¹⁴

Another case described marked improvement in the NP of a patient with psoriasis and PsA unresponsive to methotrexate. Acitretin 25 mg/day obtained significant of NP was found as early as 2 months of therapy.¹⁵

In 2009, Tosti et al evaluated the efficacy of low-dose acitretin therapy in the treatment of isolated NP in 36 patients.¹⁶ Patients received 0.2 or 0.3 mg/kg per day of acitretin for 6 months. NAPS and mNAPS scores before therapy, every 2 months during therapy, and 6 months after treatment were evaluated. The mean percentage of reduction of the NAPS score after treatment was 41%; the mean percentage of reduction of the mNAPS score of the target nail was 50%. Complete or almost complete clearing of nail lesions was achieved in 25% of patients. Ricceri et al¹⁷ described the case of a 73-year-old female with psoriatic nail disease involving all her fingernails and toenails who had previously been prescribed topical treatments, without any efficacy. Treatment with acitretin 25 mg/day in association to 5% urea nail lacquer was started. After 2 months of treatment, there was a marked improvement. No systemic side effects were observed except for cheilitis. The patient was followed up for 5 months without signs of relapse.¹⁷ Another study was conducted to evaluate the effect of acitretin treatment on the morphological nail changes in patients with NP. A total of 41 patients with NP started acitretin 0.6 to 0.8 mg/kg per day, for six months and 28 people in the control group were included in the study. Both groups had ultrasound (US) examination of fingernails. US examination was conducted before starting the treatment and after six months. After six months of treatment, there was a reduction in the thickness of the nail bed and nail matrix. The thickness of the nail plates decreased, although it was not statistically significant, and it was higher than in the control group.¹⁸

A recent report described the case of a patient with widespread nail involvement mainly on both feet and right hand with associated paronychia unresponsive to ixekizumab.¹⁹ The modified NAPS score was 45. After discontinuation of ixekizumab, treatment with acitretin 0.3 mg/kg was started. After 14 months, there was marked improvement in all nails, with an 80% reduction in mNAPS (score = 9).¹⁹

However, an additional study in the literature reported a worsening of NAPS in a group of NP patients receiving acitretin therapy.²⁰ Twenty patients completed the study. The initial dose of acitretin was 0.3 mg/kg/day for 30 days and was later raised to 0.5 mg/kg/day. NAPS was collected in the first evaluation, after 2 and 4 months. Nails of both hands were evaluated. Mean NAPS at baseline was 20 and the final score 20.5. Seven patients worsened in the final score. Three patients improved 50% of the initial NAPS and only one had an improvement of 75%.²⁰

Methotrexate

Methotrexate (MTX) is still one of the most frequently used systemic treatments for psoriasis worldwide. MTX is suggested to act primarily as an anti-inflammatory and immunosuppressant drug.²¹

Gumusel et al evaluated the use of MTX and cyclosporine in patients with NP in a single blind, randomized study.²² Patients received either oral MTX or cyclosporine for a total of 24 weeks. The study found that both therapies were effective options. The mean percentage reduction in NAPS for MTX and cyclosporine was 43.3 and 37.2%, respectively.²²

A retrospective study observed 39 patients with psoriasis and psoriatic onychodystrophy treated with MTX – parenteral administration of 25 mg (once a week). During the total treatment course, the patient received 120 mg. Local treatment was also provided using urea-based nail lacquer (once a day for 6 months). The survey revealed that at 7 weeks of treatment there was a 25% reduction of baseline NAPS, at 14 weeks of therapy the above-mentioned score was reduced to 50% and at the 24 weeks for 75%, respectively.²³

Another prospective controlled study of 87 psoriatic patients with nail involvement compared the efficacy of MTX, biologic agents (etanercept, infliximab and adalimumab), narrowband UV-B phototherapy, acitretin, and no treatment. Mean improvements after 16 weeks using the NAPS score were 13.9% with MTX, 78.4% with biologic agents, 30.7% with narrowband UV-B phototherapy, and 9.1% with acitretin.

None of the conventional treatment agents caused any statistically significant difference on NAPS at the end of week 16 compared with control group, although PASI decreased significantly. Rate of NAPS changes was more prominent in

the biological treatment group, and a statistically significant difference was detected when compared with the control group. No severe side effects were reported.²⁴

In the Tight Control of Psoriatic Arthritis (TICOPA) study, patients were treated with MTX with rapidly escalating doses (15 mg/week for 4 weeks, 20 mg/week for 2 weeks, and 25 mg/week thereafter if tolerated). A total of 117 patients had nail involvement. At 12 weeks, the median change in modified mNAPSI score was -2 (interquartile range -8 to 0), the median change in the nail plate score was 0 (interquartile range -3.75 to 1), and the median change in the nail bed score was -1 (interquartile range -4.75, 0).²⁵

In a double-blind study, 851 patients with PsA were randomized to 1 of 3 treatment arms, as follows: oral MTX (20 mg) plus subcutaneous placebo given weekly (n = 284), subcutaneous etanercept (50 mg) plus oral placebo given weekly (n = 284), or subcutaneous etanercept (50 mg) plus oral MTX (20 mg) given weekly (combination therapy; n = 283). A total of 65.1% of patients in the MTX monotherapy group had an mNAPSI greater than 0 at baseline. At 24 weeks, the mean change from baseline was -1.1 ± 0.2 , with 38.8% of patients achieving a score of 1. In etanercept monotherapy group, the mean change from baseline was -1.5 ± 0.2 ; meanwhile in the combination therapy group mean change was 1.7 ± 0.2 .²⁶

In a prospective, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (METOP) participants were randomly assigned to receive either MTX at a starting dose of 17.5 mg/week or placebo for the first 16 weeks, followed by methotrexate treatment of all patients up to 52 weeks. The study examined the effect of MTX on NP, using the NAPSI score of the worst fingernail as the target nail. At baseline mean NAPSI score was 4 (range 1–8). At 16 weeks, the MTX group had a reduced NAPSI score, compared with no change in the placebo group. At 52 weeks, complete clearance of nail disease was seen in 14% of patients with active NP at baseline. These results suggest that MTX may have a beneficial effect in nail disease. However, the response is likely to be slow, due to the slowing of nail growth.²⁷

Another study was conducted to determine whether the data obtained in the METOP-trial correspond to real-life registry data from the Swiss Dermatology Network for Targeted Therapies (SDNTT). Data of 449 patients with moderate to severe psoriasis who participated in the SDNTT registry between 2011 and 1st of July 2017 were analyzed. Only patients receiving MTX s.c. were included. A total of 66 patients under MTX were enrolled. The study found that NP improved from a mean NAPSI of 16.4 to 13.0 after 12 weeks. Compared to the METOP-trial, the response rates seen in the real-life cohort were found to be lower.²⁸

Lee et al report a case of severe psoriatic nail dystrophy involving all 20 nails successfully treated by low dose MTX. Nail lesions were unresponsive to topical clobetasol propionate and calcipotriol. Therefore, low dose of MTX (5 mg per week) was initiated. A good response with emergence of normal plate proximally was achieved as early as 4 weeks, while complete resolution of the severe nail dystrophy was achieved after 9 and 13 months of MTX therapy for fingers and toes, respectively.²⁹

Cyclosporine

Cyclosporine is an immunomodulatory drug that binds cyclophilin and inhibits calcineurin, preventing activation of IL-2 and therefore decreasing T-cell activation.³⁰ Feliciani et al conducted a study to evaluate a combination of cyclosporine and topical calcipotriol cream versus cyclosporine alone. Fifty-four patients affected by severe psoriasis and nail involvement were selected and matched for severity of nail involvement, sex, age, and cyclosporine dosage. Group A included 21 patients treated with cyclosporine alone (3.5 mg/kg/day) for three months while group B included 33 patients treated with the same cyclosporine dosage plus, for the same time, topical application of calcipotriol cream twice a day. Both cyclosporine along the cyclosporine combined with topical calcipotriol twice a day were useful for treating NP after three months of therapy although the combined therapy showed a better overall result in both mild and severe NP. After three months, in 26 out of 33 patients (79%) NP showed a marked improvement. In the cyclosporine alone group, improvement was found in 10 of 21 (47.6%).³¹ A prospective 12-month, nonrandomized, unblinded clinical trial of 57, 58, and 55 patients who received cyclosporine (2.5–3.75 mg/kg/day), adalimumab (40 mg every other week), or combination, respectively was conducted to assess the efficacy and safety of adalimumab or cyclosporine as monotherapy or combination therapy for patients with active PsA. A total of 44% of patients treated with cyclosporine, 56% of patients treated with adalimumab, and 100% treated with a combination of both achieved reduction of 50% in NAPSI

score (NAPSI50), suggesting that combination therapy of a TNF- α inhibitor and cyclosporine was safe and highly effective, with no increase in adverse events.³²

Sánchez-Regaña et al performed a retrospective study of 84 patients with moderate–severe psoriasis on the effectiveness of systemic treatments (conventional and biological therapy). All patients had been treated with one or more of the following regimens: continuous oral therapy with acitretin, continuous or intermittent therapy with oral or subcutaneous MTX, continuous or intermittent oral therapy with cyclosporine, intermittent therapy with PUVA, intermittent therapy with NUVB (narrow band UVB), REPUVA (oral administration of acitretin and PUVA treatment) and RENUVB (oral administration of acitretin and NUVB treatment), continuous subcutaneous therapy with efalizumab, intermittent and continuous subcutaneous therapy etanercept, continuous intravenous therapy with infliximab or continuous subcutaneous adalimumab therapy. The mean baseline NAPSI score was 14.7, respectively. Scores were recorded at baseline and at weeks 12, 24 and 48 of follow-up. NP improved in all patients. The NAPSI score fell significantly in all tests ($p < 0.001$), with conventional treatments (from 12.7 to 9.7; to 6.0 and to 4.2) and with biological treatments (from 17.5 to 11.2; to 4.7 and to 1.9). Nonetheless, the percentage of change in the NAPSI score was significantly higher ($p < 0.001$) with biological treatments at 12, 24 and 48 weeks. All the anti-psoriatic agents obtained a significant reduction ($p < 0.05$) in the mean NAPSI score at 12, 24 and 48 weeks, except NUVB. In classical treatment group, the reduction was significantly higher in the patients treated with cyclosporine ($p < 0.01$) than in those treated with acitretin, MTX, PUVA, NUVB and RENUVB. In the biological treatment group, although the percentage of reduction in the NAPSI score was significantly greater with infliximab and adalimumab at 12 and 24 weeks, the differences between biological treatments disappeared at 48 weeks.³³

Dimethylfumarate

Dimethylfumarate (DMF) is an orally administered fumaric acid ester with immunomodulating, anti-inflammatory, and anti-oxidative effects approved for the treatment of moderate-to-severe plaque psoriasis.³⁴ Despite having been approved for several years, there is a paucity of published literature evaluating its use in NP.

An interim analysis of the prospective, noninterventional SKILL study summarized results of DMF treatment regarding effectiveness (overall and in impactful areas) and safety. Data from 676 patients suffering from moderate-to-severe plaque psoriasis were analyzed after 52 weeks of DMF treatment. Of these, 257 had data available after 52 weeks. The considered impactful areas were nails, palms, soles, and scalp. The mean nail-Physician Global Assessment (nail-PGA) of patients with nail disease at baseline (nail-PGA > 0) improved from 1.8 (95% CI 1.7–1.9) at baseline to 0.6 (95% CI 0.4–0.8, $p < 0.001$) at week 52. Of the patients presenting with nail involvement at baseline, 50.6% (95% CI 46.3–67.0%) were clear (nail-PGA of 0) at week 52, and 70.2% of patients experienced an improvement of their nail involvement until week 52.³⁵

Vlachou et al described the case of a patient who suffered from plaque psoriasis and psoriatic nail involvement. His skin has responded well to phototherapy and cyclosporine in contrast to his psoriatic nail dystrophy. Tacrolimus ointment 0.1% applied around his nails once daily, in addition to the cyclosporine, improved the nail pitting slightly after 5 months, but the onycholysis remained unchanged. Cyclosporine was discontinued after a total of 10 months as the limited benefit on the nail psoriasis did not justify the potential toxicity. He was then started on DMF 30 mg, two tablets twice daily. This was gradually increased at 2-week intervals to DMF 120mg, one tablet three times daily. The first improvements in onycholysis were recorded at month 2, with definite improvement at month 5 of follow-up. Adverse events included flushing and abdominal pain and a stable decrease in lymphocyte count.³⁶

Phototherapy and Photochemotherapy

Phototherapy with narrow-band UVB (NB-UVB), and photochemotherapy with UVA in addition to the photosensitizer psoralen (PUVA) are well-established treatments for cutaneous psoriasis. In a prospective series of ten patients with 26 individual nail dystrophies treated with oral PUVA therapy using 8-methoxypsoralen at a dose of 0.6 mg/kg 2–3 times a week, 70% showed improvement in nail changes such as onycholysis, subungual hyperkeratosis, nail plate crumbling, and oil-drop discoloration. None had improvement in pitting.³⁷

Another small prospective study demonstrated considerable improvement in four out of five patients given topical PUVA 2–3 times a week using 1% solution of 8-methoxypsoralen applied to the proximal nail fold up to the terminal

phalanx, with onycholysis showing greater response than pitting. There was no incidence of adverse effects in either study.³⁸

The extent to which UVA and UVB radiation can penetrate in normal human cadaveric nail plate has also been examined. All 10 fingernails completely blocked the UV-B light, while the mean penetration of UV-A light through the fingernails was 1.65%.

It was found that the nail plate completely blocked UVB, and the penetration of UVA was minimal. These data suggest that therapeutic efficacy of phototherapy may be compromised by the nail plate. This minimal penetration of UV-A light may explain why therapies such as psoralen-UV-A (PUVA) have low efficacy for the treatment of NP.³⁹

Biologic Therapy and Small Molecules

Regarding biologic and small molecules used to treat NP, multiple systemic therapies have been studied in the treatment of nail psoriasis.¹²⁴ Some of these studies are discussed in the following paragraphs.

Phosphodiesterase-4 Enzyme (PDE-4) Enzyme Inhibitor

Apremilast

Apremilast is a small-molecule inhibitor of phosphodiesterase 4 with an intracellular mechanism of action that increases levels of cyclic adenosine monophosphate (cAMP) indicated for the treatment of moderate to severe plaque psoriasis and for the treatment of PsA.⁴⁰ In 2016, the ESTEEM 1 and 2 phase III RCTs explored the use of apremilast in patients with difficult-to-treat areas, including NP.⁴¹ A total of 824 patients with NP were randomized 2:1 to receive apremilast 30 mg twice daily or placebo and at week 16, those on placebo were switched to apremilast, followed by a randomized withdrawal phase at week 32. At week 16, apremilast produced greater improvement in NAPSI index versus placebo in both studies [mean NAPSI percentage improvement of 22.5% vs -6.5% ($p < 0.0001$) and 29.0% vs 7.1% ($p = 0.0052$) for ESTEEM 1 and 2, respectively]. A negative percentage here implies a worsening in NAPSI. A significantly greater proportion of patients on apremilast achieved a NAPS-50 score (50% reduction from baseline in NAPS score) at week 16 versus placebo [33.3% vs 14.9% ($P < 0.001$) and 44.6% vs 18.7% ($P < 0.001$) for ESTEEM 1 and 2, respectively]. Patients who received apremilast 30 mg twice daily continued to show improvement at week 32 with a mean NAPS percentage improvement of 43.6% and 60.0% in ESTEEM 1 and 2, respectively. Patients who were re-randomized from placebo to apremilast 30 mg at week 16 showed improvement in mean NAPS percentage change at week 32 (24.6 and 47.6% in ESTEEM 1 and 2, respectively). Through week 52, patients in ESTEEM 1 and 2 who had a PASI response at week 32 (ESTEEM 1: C 75% reduction from baseline/ESTEEM 2: C 50% reduction from baseline) continued to show improvement in nail psoriasis at week 52. The mean percentage reduction from baseline in target nail NAPS score for these patients, who either received apremilast 30 mg initially or were re-randomized from placebo to apremilast at week 32 ranged from 60 to 64%. The LIBERATE study evaluate long-term efficacy and safety of apremilast in biologic-naïve patients with moderate to severe plaque psoriasis and safety of switching from etanercept to apremilast.⁴² A total of 250 patients were randomized to placebo, apremilast 30 mg twice daily or etanercept 50 mg weekly through Week 16; thereafter, all patients continued or switched to apremilast through Week 104 (extension phase).⁴² The apremilast-extension phase (Weeks 16–104) included 226 patients in the placebo/apremilast ($n = 73$), apremilast/apremilast ($n = 74$) and etanercept/apremilast ($n = 79$) groups, and at Week 104, NAPS mean change from baseline was -48.1% to -51.1 AEs in $\geq 5\%$ of patients (diarrhoea, nausea, nasopharyngitis, upper respiratory tract infection and headache) did not increase with prolonged apremilast exposure.⁴²

An open-label, single-arm, real-life study was conducted to evaluate efficacy and safety of treating nail psoriasis using apremilast (30 mg twice daily) for 52 weeks.⁴⁸ Eleven patients were recruited. mNAPS75 response, 75% or greater reduction over baseline mNAPS, was reached by 27.2% of patients at week 12, 36.4% at week 36 and 45.5% at week 52. Gastrointestinal AEs were the most common, followed by upper respiratory infections.⁴³

Muñoz-Santos et al⁴⁴ evaluated efficacy, US parameters and safety of apremilast for NP conducting a prospective cohort study including adult patients with plaque and NP with a NAPS score of 12 or more. Patients were treated with apremilast 30 mg b.i.d. for 52 weeks. Forty-five patients were included. At week 52 NAPS improved by 53%. US parameters improved from week 16 onwards. Target nail NAPS improvements were higher for nail matrix scores (60%)

than for nail bed scores (38%, $p < 0.001$). Safety was consistent with the known apremilast profile.⁴⁴ Another article reported the cases of two patients affected by NP successfully treated with apremilast.⁴⁵ In one patient, all ten nails of the hands were affected reaching a NAPS I of 44. After a month of treatment with apremilast, the patient showed a significant amelioration of pruritus and scaling. At week 16, there was a remarkable improvement in nail findings, achieving a NAPS I of 4 (improvement of 90%). The other patient was affected by plaque psoriasis and nail involvement with a NAPS I score of 32. He started treatment with apremilast. After six months of therapy, the patient had no significant side effects and was able to maintain a sustained response and a high level of satisfaction with the results.

Tumor Necrosis Factor Alpha Inhibitors

Etanercept

Etanercept is a fully humanized, TNF- α receptor approved for the treatment of plaque psoriasis, which acts by blocking TNF- α .⁴⁶ A 24-week randomized controlled clinical trial exploring the use of etanercept, infliximab, and adalimumab for the treatment of NP was conducted by Ortonne et al in 2013.⁴⁵ The efficacy of two dosing regimens of etanercept were compared in patients who previously failed at least one systemic therapy. Patients were randomized to the etanercept group received 50 mg twice weekly for 12 weeks followed by once weekly (BIW/QW), or 50mg once weekly for 24 weeks (QW/QW). The primary endpoint was the mean NAPS I over 24 weeks. At week 24, mean NAPS I had decreased in both etanercept groups [BIW/QW group: -4.3 ($p < 0.0001$); QW/QW group: -4.4 ($p < 0.0001$)]. Mease et al²⁶ examined the efficacy of MTX monotherapy relative to that of etanercept monotherapy and their combination in 588 patients. There was no significant difference in mNAPS I changes between the two monotherapies at week 24, while combining therapy showed a greater decrease in mNAPS I compared with MTX monotherapy (-1.7 vs -1.1, $p = 0.02$). Another study evaluated the sustained improvement of nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis.⁴⁷ Of 711 patients treated with etanercept, 79% reported NP at baseline. NAPS I scores decreased from 4.64 at baseline to 3.30 at week 12, presenting an improvement of 28.9% ($p < 0.001$). Similarly, an improvement in NAPS I of 2.38 (51%) was noted at week 54, with 30% of the patients with NP reporting no signs of it at the end of treatment. Rallis et al⁴⁸ case of a 35-year-old man with plaque psoriasis and psoriatic lesions in all 10 fingernails who was treated with etanercept. After 3 weeks' administration of etanercept, a marked improvement was noted, whereas a complete cure was seen during the sixth month of treatment. In a retrospective, observational study, 66 patients with moderate to severe plaque psoriasis were treated with etanercept following the summary of product characteristics, that is, at 25 or 50 mg twice weekly for a maximum of 24 weeks.⁴⁹ At week 12, all patients who began treatment at 50 mg had their dose reduced to 25 mg. NP was significantly improved after 24 weeks of treatment, both in the total sample and in the 2 subpopulations. No significant differences were noticed between the doses during any week of the study. There is also a report of two cases with plaque psoriasis and involvement of all fingernails⁵⁰. The first patient was treated with etanercept 50 mg twice a week for 12 weeks, followed by etanercept 50 mg once a week through week 48. NAPS I score (0–80) was reduced from 56 at baseline to 4 at week 48, improved by 92.9%. The second patient, which was previously treated with efalizumab, switched to etanercept 50 mg twice a week for 12 weeks and then was placed to etanercept 25 mg twice a week through week 48. NAPS I score (0–80) was reduced from 53 at baseline to 30 at week 48, improved by 56.6%. Additionally, there is another case report of a male with moderate plaque psoriasis and concomitant nail dystrophy in all his finger and toenails, who was treated with etanercept 50 mg on a weekly basis.⁵¹ Almost total resolution of the lesions on the fingernails was seen within 6–9 months of treatment and marked improvement in the toenails after 12 months of therapy. Recently, Niebel et al reported the rare concomitant clinical presentation of PsA and annular atrophic lichen planus on the trunk of a male patient. The patient's fingernails and toenails also presented psoriatic manifestations including crumbling, pitting, and oil drops. After failure of the disease modifying antirheumatic drugs (DMARDs), therapy with subcutaneous etanercept 50 mg once weekly was initiated. The patient experienced a significant improvement of both skin and joint complaints. Nail lesions also underwent a significant improvement.⁶⁹

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody that binds TNF- α and is approved for the treatment of moderate to severe plaque psoriasis and PsA.⁵³ In an open-label, prospective study, 25 patients who suffered from plaque psoriasis (n

= 9) or PsA (n = 16) and had nail involvement (NAPSI > 14) received intravenous infusions of infliximab (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter, through week 22.⁵⁴ In the plaque psoriasis group, mNAPSI was reduced from 28.3 ± 15.1 at baseline to 13.8 ± 7.3 at week 14. Similarly, in the PsA group mNAPSI was reduced from 33.3 ± 13.4 at baseline to 16.4 ± 8.2 at week 14. Therefore, all patients showed a 50% reduction of the initial mNAPSI. Moreover, at week 22, mNAPSI was 0 for both groups ($p < 0.001$), indicating a clinical remission of NP (NAPSI75) in all patients.⁵⁴ Fabroni et al performed an open-label retrospective study considering 48 psoriatic patients presenting recalcitrant nail involvement and receiving infliximab.⁵⁵ NAPSI scores at 0, 14, 22 and 38 weeks and percentage of patients achieving NAPSI-50,-75,-90 at 14, 22 and 38 weeks were calculated. At baseline, the mean NAPSI $\pm$ SD was 49.68 ± 25.99 . The mean NAPSI $\pm$ SD got down to 18.58 ± 9.42 at week 14, to 9.54 ± 4.71 at week 22 and further down to 7.21 ± 4.92 . Complete nail clearing was observed in five (10.4%) patients. A cohort of 41 (85.4%), 46 (95.8%) and 47 (97.9%) patients achieved NAPSI50 at weeks 14, 22 and 38, respectively. A cohort of 11 (22.9%), 31 (64.6%) and 39 (81.25%) subjects reached NAPSI75 at weeks 14, 22 and 38, respectively. Of the patients, 1 (2.08%), 11 (22.9%) and 14 (29.2%) reached NAPSI-90 at weeks 14, 22 and 38, respectively. In an open-label study, 18 psoriatic patients with nail involvement were selected to receive infliximab intravenously at its regular-dose scheme.⁵⁶ NAPSI score was assessed at baseline and at weeks 14, 22, 30, and 38. A significant ($p < 0.01$) reduction of mNAPSI was noted from 55.78 ± 18.57 at baseline to 29.83 ± 13.73 at week 14, to 16.33 ± 10.43 at week 22 and to 7.33 ± 7.35 at week 30. At week 38, an almost complete resolution of psoriatic nail lesions was observed with the mNAPSI score being 3.28 ± 4.84 . In a Phase III, multicenter, double-blind trial (EXPRESS trial), 378 patients with moderate to severe plaque psoriasis received infusions of either infliximab 5 mg/kg or placebo at weeks 0, 2, and 6, then every 8 weeks to week 46.⁵⁷ At week 24, placebo-treated patients crossed over to infliximab treatment. The percentage improvement from baseline of the NAPSI was significantly greater in infliximab-treated patients than in placebo-treated patients at weeks 10 (26.0 ± 42.3 vs -5.9 ± 54.3 ; $p < 0.0001$) and 24 (56.3 ± 43.4 vs -3.2 ± 62.3 ; $p < 0.0001$). Improvement of NP achieved at week 24 in infliximab-treated patients was maintained at week 50 ($56.3 \pm 52.0\%$).

An open, 24 weeks, prospective study evaluated NP in patients treated with adalimumab, etanercept or infliximab. NAPSI was assessed at baseline, week 14, and 24. Sixty patients were included in the study. The mean NAPSI was 33.77. In the adalimumab group, the mean NAPSI score was 33.1 (± 14.9) at baseline, 21 (± 8.91) at week 14 and 11.4 (± 4.6) at week 24 ($p < 0.0002$). In the etanercept group, the mean NAPSI was 34.8 (± 12.38) at baseline, 23.6 (± 10.43) at week 14, and 10.6 (± 5.25) at week 24 ($p < 0.0016$). In the infliximab group, the mean NAPSI was 33.3 (± 9.76) at baseline, 14.9 (± 4.20) at week 14 ($p < 0.001$) and 3.1 (± 3.27) at week 24 ($p < 0.00001$). At week 14 infliximab showed a superior efficacy compared to adalimumab and etanercept ($p < 0.05$).⁵⁸ [Safa et al presented a case of a male with plaque psoriasis and nail disease involving four fingernails.⁵⁹ Subject was administered infliximab at the regular dose at weeks 0, 2, and 6. A marked improvement of NP was seen after the second infusion, while subject remained free of lesions after the third infusion. There is also a report of two cases with nail NP that responded to infliximab.⁶⁰ The first case had nail involvement of all finger and toenails. The initial NAPSI score of 24 became 3 after the third infusion of infliximab. The second patient who had NP in all 20 nails was also treated with infliximab. After a single infusion, patient's NAPSI score of 22 fell to 6. However, the development of paresthesia of the arms and legs after the second infusion resulted in infliximab cessation.

Another article reported the case of a patient with a 4-year history of plaque psoriasis and severe nail dystrophy in all fingernails and toenails. He had previously been treated with oral cyclosporine and topical steroids, which were effective for the skin lesions, but not the nail lesions. The NAPSI score was 64. Adalimumab was started and interrupted five months later due to inefficacy on the nail lesions. The patient was then switched to infliximab at a dose of 5 mg/kg, i.v. administered at week 0, 2, 6 and then every 2 months. Nine months after initiation of infliximab, all dystrophic nail lesions had greatly improved (NAPSI score 8). The authors suggested that systemic administration of infliximab raised blood drug concentration more promptly than subcutaneously injected adalimumab, contributing to the recovery of a normal nail cycle.⁶¹

Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody that binds TNF- α approved for psoriasis and PsA.⁶²

Irla et al reported two cases of NP under adalimumab monotherapy (80 mg loading dose and thereafter 40 mg every other

week).⁶³ The first patient showed a reduction of the NAPSI score from 8 at baseline to 3 at month 6. Accordingly, the second patient presented a reduction of the NAPSI score from 8 at baseline to 3 at month 8. In an open, nonrandomized study, 21 patients were scheduled to receive adalimumab at a dose of 80 mg at baseline, 40 mg at week 1, and 40 mg every 2 weeks thereafter.⁶⁴ Seven patients suffered from severe plaque psoriasis with nail involvement and 14 patients suffered from PsA, cutaneous psoriasis, and nail involvement. NAPSI score was assessed at baseline, at weeks 12 and 24. Treatment was well tolerated, and significant improvement was observed in all patients after the eighth injection. In patients with only cutaneous lesions, mean NAPSI score decreased from 10.57 ± 1.21 for the fingernails and 14.57 ± 2.50 for the toenails at baseline to 5.57 ± 0.78 and 9.57 ± 2.17 at week 12, and to 1.57 ± 0.20 and 4.14 ± 1.58 at week 24, respectively. In patients with PsA, mean NAPSI score decreased from 23.86 ± 2.00 for the fingernails and 29.29 ± 2.87 for the toenails at baseline to 12.86 ± 1.05 and 19.21 ± 2.07 at week 12, and to 3.23 ± 0.32 and 10.00 ± 1.40 at week 24, respectively.⁶⁴ In a single-center, retrospective study, 15 patients with moderate to severe plaque psoriasis, resistant to previous conventional systemic treatments or other biological agents, received adalimumab (80 mg loading dose and thereafter 40 mg every other week).⁶⁵ The NAPSI score decreased from an initial value of 18.9 ± 12.2 to 8.2 ± 4.7 at week 24 ($p = 0.001$). In a post hoc analysis, 730 patients with or without a history of PsA and moderate to severe psoriasis were randomized to adalimumab plus adjunctive topical therapy or adalimumab monotherapy.⁶⁶ The mean NAPSI scores for the fingernails were improved from baseline to week 16 in patients with initial nail involvement, regardless of their baseline PsA status. However, numerically larger but not statistically significant decreases in mNAPSI scores were observed over time for patients without a history of PsA compared to patients with a history of PsA. Another post hoc analysis on 730 patients, of whom 457 (63.1%) and 433 (60.1%) had NP, or scalp both, respectively, showed NP improvement demonstrated by a median decrease from baseline NAPSI at week 16 of 39.5% ($9.4 \pm 164.5\%$).⁶⁷ Elewski et al conducted a phase III randomized controlled study evaluating the efficacy and safety of adalimumab specifically for the treatment of NP. Patients received 40 mg adalimumab every other week or placebo, with the primary endpoint being a NAPSI75 score at week 26. The primary endpoint was met in 46.6% of patients versus 3.4% of placebo patients ($p < 0.001$).⁶⁸ Safety and efficacy of adalimumab long-term treatment (52 weeks) was evaluated in a phase-3, randomized trial in patients with moderate-to-severe plaque psoriasis and concomitant moderate-to-severe fingernail psoriasis.⁶⁹ Of the 109 patients treated, 54.4% achieved NAPSI75 at week 52. Leonardi et al compared adalimumab vs placebo in 72 patients.⁷⁰ The mean percentage improvement in NAPSI score was significantly greater for adalimumab than for placebo (50 vs 8%, $p = 0.02$) at week 16. Kokolakis et al conducted a multicentre prospective study in which 267 patients with nail involvement were treated with adalimumab for a period of 24 months.⁷¹ After 3 and 6 months, reductions in NAPSI of 32.8% ($p < 0.001$) and almost 50% ($p < 0.001$), respectively, were observed, compared with baseline scores (mean NAPSI score, 34.2 ± 1.3). In 6 months, 60.0% of patients achieved NAPSI50, 36.4% NAPSI75, and 21.7% NAPSI90. Approximately 42% and 60% of patients achieved NAPSI90 after 12 and 24 months, respectively.

Another study suggested that the contribution of TNF- α may be stronger than that of IL17A in enthesitis and the subsequent nail lesions.⁷² The authors reported the case of Japanese man with PsA and nail lesions on both hands. He was previously treated with oral etretinate (20 mg/day) for 2 months and a successive 3 years of oral cyclosporine treatment (100–150 mg/day), with only marginal improvement in the joint pain and nail lesions. Then, the patient was started on secukinumab (300 mg every 4 weeks). After 14 cycles of secukinumab treatment, although the skin lesions and joint pain disappeared, the nail lesions still showed a scant response. Therefore, the treatment was switched from secukinumab to adalimumab (80 mg every 2 weeks). Adalimumab treatment started to improve nail lesions after three cycles, and nail lesions further improved after 11 cycles of treatment. While secukinumab was effective in skin lesions, it was less effective in nail lesions, which was improved by switching to adalimumab.⁷²

The same authors described a similar case of a patient with PsA where nail lesions and skin lesions showed inverse responses to an anti-IL-17A antibody (ixekizumab) and an anti-TNF- α antibody (adalimumab), respectively. Ixekizumab (80mg every 4 weeks) completely suppressed the skin lesions but exerted limited effects on nail lesions after the 19th cycle, while switching to adalimumab induced significant improvement of nail lesions. Clinical improvement of nail lesions was observed after five cycles of adalimumab treatment, but skin lesions recurred, which were well controlled by topical steroid therapy. The authors state that the inverse clinical responses of the skin lesions and nail lesions to

ixekizumab and adalimumab endorse the concept that IL-17A and TNF- α are primarily involved in skin lesions and enthesitis in PsA, respectively.⁷³

Certolizumab

Certolizumab pegol is an inhibitor of tumor necrosis factor- α (TNF- α) approved for the treatment of moderate-to-severe psoriasis.⁷⁴ Mease et al included 409 patients with PsA treated with certolizumab pegol vs placebo.⁷⁵ At baseline, 73.3% of patients had nail disease, and after a treatment period of 24 weeks, mNAPSI changed from baseline was -1.6 for the group treated with certolizumab pegol every 2 weeks and -2.0 for the group treated with certolizumab pegol every 4 weeks compared with -1.1 for the placebo group ($p = 0.003$ and $p < 0.001$, respectively).

Mazzeo et al reported the experience with 8 patients with PsA and psoriatic nail damage treated with certolizumab pegol in the standard dosing of 400 mg at weeks 0, 2 and 4 at weeks 0, 2 and 4, followed by 200 mg every 2 weeks.⁷⁶ NAPSI improved from 50.34 (baseline) to 20.5 (W24) with a further reduction to 10 (W52). A real-life multicenter study evaluated the effectiveness and safety of certolizumab in patients with psoriasis and PsA in clinical practice.⁷⁷ In this retrospective study, patients received subcutaneous certolizumab (400 mg loading dose at 0, 2 and 4 weeks, followed by 200 mg every 2 weeks) for up to 52 weeks. Primary outcomes included mNAPSI score. Among patients with NP ($n = 56$), there were significant decreases in mNAPSI mean score from a baseline at all time points. The baseline mNAPSI score was 14.64, with changes from baseline of -5.69 at week 12, -8.77 at week 24 and -12.92 at week 52.

Moreover, certolizumab dosed at 400 mg every 2 weeks (Q2W) and 200 mg Q2W over 52 weeks resulted in improvements in Japanese patients with moderate to severe plaque psoriasis.⁷⁸ Reductions in mNAPSI score were observed for both certolizumab-treated groups from baseline to week 16, and these were maintained through to week 52. At week 52, there was a mean (standard deviation; SD) decrease of -3.7 (2.7) and -3.0 (2.1) in the certolizumab 400 mg Q2W and CZP 200 mg Q2W groups, respectively.

Golimumab

Golimumab is TNF- α inhibitor approved for the treatment of rheumatoid arthritis, PsA, and ankylosing spondylitis.⁷⁹ The GO-VIBRANT trial evaluated the efficacy of golimumab for the treatment of NP associated with PsA.⁸⁰ A total of 480 patients were randomized to receive either intravenous (IV) golimumab 2 mg/kg at week 0, 4, and then every 8 weeks through week 52, or placebo with crossover at week 24. At baseline, mean mNAPSI score was 18.6. The mean improvement from baseline in mNAPSI score was significantly greater in patients treated with golimumab versus those treated with placebo at week 14 (-9.6 vs -1.9 , $p < 0.0001$) and week 24 (-11.4 vs -3.7 , $p < 0.0001$). At week 52, mNAPSI response was maintained in patients randomized to receive golimumab (-11.4 at week 24 and -12.1 at week 52) and increased numerically (from -3.7 to -12.9) in patients who crossed over from placebo to golimumab at week 24. Kavanaugh et al used subcutaneous injection of 50 mg golimumab vs placebo on 405 patients with PsA. The median improvement in NAPSI score from baseline to weeks 14 and 24 was significantly greater ($p < 0.001$) in the golimumab 50 mg group (25, 43%) and the golimumab 50 mg group (33, 54%) compared to that in the placebo group (0, 0%, respectively).⁸¹ Vieira-Sousa et al evaluated MTX monotherapy or combination therapy with subcutaneous injection of 50 mg golimumab in 44 patients.⁸² After 12 weeks of treatment, the medium percentage of reduction in target fingernails NAPSI score (0–8) from baseline for combination therapy was greater than that of methotrexate monotherapy (-2 vs 0, $p = 0.044$).

Jung reported the case of NP improved with golimumab in a patient affected by PsA.⁸³ Fifty mg of golimumab per month were administered subcutaneously. After the third injection, there was no further pain or tenderness of the joints. The patient's nails gradually improved, and no new lesions were observed after 24 months.

Interleukin-12/23 Inhibitors

Ustekinumab

Ustekinumab is a human, monoclonal antibody that binds the shared p40 subunit of IL-12 and IL-23 and prevents the cytokines from binding their respective receptors.⁸⁴ In 2010, Rallis et al reported a case of man who suffered from plaque psoriasis and psoriasis of four fingernails.⁸⁵ The patient was treated with ustekinumab and underwent a marked

improvement of his NP, after the first injection at week 4. A complete resolution was observed at week 8, four weeks after the second injection. Later, an open-label, prospective study was conducted on 27 patients with plaque psoriasis and fingernail involvement.⁸⁶ The participants received subcutaneous injections of ustekinumab at a dose of 45 mg at baseline (week 0) and week 4 and every 12 weeks thereafter. Alternatively, 90 mg could be used in patients with body weight greater than 100 kg. NAPSI score was assessed at baseline and at weeks 4, 16, 28, and 40. The mean NAPS score was significantly ($p < 0.001$) decreased from 19.59 ± 7.92 at baseline to 16.96 ± 6.99 at week 4, 9.70 ± 4.47 at week 16, 3.85 ± 3.03 at week 28, and 2.00 ± 2.33 at week 40. In an open-label, uncontrolled, nonrandomized study, a total of 27 patients suffering from moderate-to-severe plaque psoriasis who had nail involvement received subcutaneous injections of ustekinumab at a dose of 45 mg (or 90mg if $>100\text{kg}$) at baseline and week 4 and every 12 weeks thereafter.⁸⁷ NAPS score was assessed at baseline at weeks 16, 28, and 40. NAPS median score was significantly ($p < 0.0001$) decreased from 73.0 (range: 12.0–151.0) at baseline to 37.0 (range: 7.0–92.0) at week 16, to 9.0 (range: 0.0–32.0) at week 28 and to 0.0 (range: 0.0–12.0) at week 40. Moreover, NAPS median score was significantly ($p < 0.0001$) improved, compared to baseline, by 42.5% (range: 21.9–64.9%) at week 16, by 86.3% (range: 75.0–100.0%) at week 28, and by 100.0% (range: 91.0–100.0%) at week 40. In a double-blind, placebo-controlled study to assess the safety and efficacy of ustekinumab in patients with moderate-to-severe psoriasis, 158 patients were randomized to receive ustekinumab 45 mg ($n = 64$) or 90 mg ($n = 62$) at weeks 0, 4, and every 12 weeks, or placebo ($n = 32$) with cross-over to ustekinumab at week 12.⁸⁸ At baseline, 64.6% of patients had nail psoriasis, with a mean NAPS score of 4.0 ± 2.0 . At week 12, the mean percent improvement in NAPS was 7.7 ± 95.1 and 10.0 ± 66.1 in the ustekinumab 45 mg and 90 mg groups, respectively. However, none of these improvements were statistically significant compared to placebo group ($-2.9 \pm 27.8\%$). At week 64, the mean percent improvement in target NAPS was 56.6 ± 43.2 and 67.8 ± 37.5 for the ustekinumab 45 and 90 mg groups, respectively. A post hoc analysis of a phase IV, multicenter, open-label, real-world observational clinical trial, the MARCOPOLO study, was conducted to establish standard NAPS improvement rates in patients treated with ustekinumab.⁸⁹ Ustekinumab was administered over a period of 52 weeks. NAPS scores were recorded at baseline, 28 weeks, and 52 weeks. NAPS improvement rates were calculated to estimate the cumulative number of patients that corresponded to the proportion of PASI75 and PASI90 responders. From 102 patients evaluated, 81 patients who had NP. At week 52, PASI75 and PASI90 were achieved in 70.6% and 39.2%, and these proportions corresponded to 42% and 71% NAPS improvement rates, respectively.

The efficacy of ustekinumab treatment for toenail psoriasis was also investigated in another study.⁹⁰ Ustekinumab (45 mg) was administered to eligible patients for a total of 52 weeks at week 0, week 4, and every 12 weeks thereafter. A total of 22 patients with toenail psoriasis were included. The baseline mean toenail NAPS was 17.23 ± 11.61 . All the 10 toenails of 22 patients were evaluated six times at weeks 0, 4, 16, 28, 40, and 52. At week 52 NAPS score was <15 .

The improvement of individual toes was also analyzed. Although the big and second toes displayed substantial differences between weeks 0 and 52, other toes did not show significant changes after 52 weeks. Moreover, when analyzing post-treatment changes of the four matrix components of NAPS, only pitting showed statistically significant improvement. Similarly, oil-drop discoloration was the only characteristic of the bed component of NAPS that displayed significant changes after the ustekinumab treatment.

Another study was conducted to evaluate nail involvement as a predictor of differential treatment effects of secukinumab versus ustekinumab in patients with moderate to severe psoriasis.⁹¹ CLEAR and CLARITY^{92,93} were phase 3b trials designed as 52-week, randomised, double-blind. In both studies, patients were randomised (1:1) to receive secukinumab 300 mg or ustekinumab 45 or 90 mg (according to body weight at baseline). Patients received secukinumab at baseline and weeks 1, 2, and 3, then every 4 weeks from weeks 4 to 48, or ustekinumab at baseline and week 4, and then every 12 weeks from weeks 16 to 40. Data from patients were pooled from both studies. Overall, 886 and 891 patients received secukinumab and ustekinumab, respectively; among whom 269 (30.4%) and 265 (29.7%) patients had a history of nail involvement in the secukinumab and ustekinumab arms, respectively.⁹¹ Efficacy was evaluated by the percentage of patients reaching PASI 75 and PASI 90, as well as the percentage of patients achieving an absolute PASI of ≤ 3 , ≤ 1 , and 0. PASI 75 and 90 scores were calculated over 52 weeks; ≤ 3 , ≤ 1 and 0 values were assessed at weeks 16 and 52. Regardless of nail involvement, a higher percentage of secukinumab-treated patients versus those treated with ustekinumab obtained PASI 75 and 90 responses over 52 weeks. No significant impact of nail involvement was observed

on the efficacy of secukinumab as a similar percentage of patients with and without nail involvement reached PASI 75 and 90 responses. However, a higher proportion of ustekinumab-treated patients without nail involvement achieved PASI 75 and 90 scores than patients with nail involvement over 52 weeks. At weeks 16 and 52, secukinumab-treated patients showed higher PASI ≤ 3 responses compared with ustekinumab-treated patients, regardless of nail involvement. Within the secukinumab arm, PASI ≤ 3 responses were comparable in patients with (week 16: 87.2%; week 52: 83.4%) and without (week 16: 87.0%; week 52: 86.0%) nail involvement. In the ustekinumab arm, higher PASI ≤ 3 responses were observed in patients without nail involvement (week 16: 71.3%; week 52: 75.8%) than patients with nail involvement (week 16: 64.6%; week 52: 68.7%).

In this study, secukinumab demonstrated overall superior efficacy compared with ustekinumab in psoriasis and gave similar response rates in patients with and without nail involvement. Meanwhile, in patients treated with ustekinumab, nail involvement was associated with reduced PASI responses, prompting the suggestion that nail psoriasis acts as a predictor of inferior skin response to ustekinumab. Therefore, when considering nail involvement, secukinumab provided a better clinical outcome than ustekinumab. These results suggested that secukinumab should be preferred for the treatment of cutaneous psoriasis in patients with nail involvement.⁹¹

Another article reported the experience using ustekinumab for the treatment of psoriasis with nail involvement on 13 patients with moderate to severe psoriasis and PsA unresponsive to at least four biologics.⁹⁴ Ustekinumab was given to all 13 patients at week 0, week 4, and then subsequent doses every 12 weeks. Five of these patients received 90 mg as monotherapy because they exceeded the 220-pound weight range, and the remainder received ustekinumab 45 mg in combination with either 15–30 mg MTX weekly (six patients) or cyclosporine 100 mg twice a day (two patients). NAPSI and mNAPSI were performed at week 0, week 4, and week 12 for each patient and photographs of both hand's fingernails and the most severely affected nail (target nail) were taken at each visit. Average baseline NPSI score for the 13 patients was 22.3 and mNPSI at week 0 was 6.3. The mean NPSI score at the end of week 12 was 14.8 (range, 0–58) and the mean mNPSI score for the target nail was 5.2 (range, 0–10).

The mean percentages of reduction of the NPSI score and mNPSI score were 31.8% and 13.3%, respectively. At the end of week 12, for two of our 13 patients (15%), NPSI scores remained the same.⁹⁴ Byun et al described the case of patient affected by PsA and NP resistant to triamcinolone injections and topical betamethasone dipropionate/calcipotriol.⁹⁵ He was treated with 45 mg of ustekinumab at weeks 0 and 4, and then every 12 weeks thereafter. The initial NPSI score was 98. After the second injection of ustekinumab, notable amelioration in his nail and nail fold psoriasis was observed. A complete disappearance of nail fold psoriasis was seen at week 28 and was maintained thereafter. The NPSI score decreased to 7 at week 40. After the termination of ustekinumab treatment at week 64 at the patient's request, his NP relapsed.

Interleukin-17 Inhibitors

Ixekizumab

Ixekizumab is a monoclonal antibody that targets IL-17A being licensed for use in moderate-to-severe plaque psoriasis and PsA.^{96,97} In a placebo-controlled study with 58 patients, Leonardi et al highlighted that 75 mg/150 mg every 4 weeks (Q4W) ixekizumab markedly alleviated the clinical symptoms of NP compared with the placebo group as early as week 2.⁹⁸ The SPIRIT-P1 study compared ixekizumab with adalimumab and placebo in 417 patients.⁹⁹ Among them, 289 had NP. At week 24, the mean changes from baseline in the NPSI score were significantly greater for the ixekizumab Q4W (–14.0), ixekizumab q2w (–15.5), and adalimumab (–10.7) groups than for the placebo group (–2.4) ($p < 0.001$).⁸⁹ A head-to-head trial of 189 patients with NP revealed a significantly greater number of patients achieved NPSI = 0 with ixekizumab vs ustekinumab as early as week 16.¹⁰⁰ The UNCOVER-1 study compared ixekizumab (80mg Q2W, 80mg Q4W) to placebo in 847 patients.¹⁰¹ The mean improvements in the NPSI were 7.24, 7.19, and –2.17 points, respectively ($p < 0.001$) at week 12. The UNCOVER-2 study compared the same two doses of ixekizumab with etanercept (50 mg twice a week) and placebo in 751 patients.¹⁰¹ Treatment with ixekizumab 80 mg Q2W or Q4W resulted in an equivalent reduction in the NPSI score (8.6 and 7.39, respectively), which was significantly better than that of patients treated with etanercept (5.34 points) and placebo (0.82 points, $p < 0.001$). Kerkhof et al performed a post-hoc analysis of the UNCOVER-3 study on 809 patients with baseline NP comparing the efficacy of ixekizumab with etanercept and placebo.¹⁰² Patients received placebo,

etanercept (50 mg twice weekly), or 80 mg ixekizumab as one injection every 4 weeks (Q4W) or every 2 weeks (Q2W) after receiving a 160 mg starting dose. Ixekizumab demonstrated significant improvement in NAPS I score at week 2 vs etanercept (5.1 vs -7.9%, $p = 0.024$). At week 12, greater mean percentage NAPS I improvements were achieved in the ixekizumab versus placebo groups and in the ixekizumab versus etanercept groups in both the Q4W group [36.7 vs -34.3% (vs placebo), $p < 0.001$; 36.7 vs 20% (vs etanercept), $p = 0.0048$] and Q2W group [35.2 vs -34.3% (vs placebo), $p < 0.001$; 36.7 vs 20% (vs etanercept), $p = 0.072$]. A negative sign implies that NAPS I worsened in the placebo group. In a head-to-head trial with 368 NP patients, Mease et al compared ixekizumab with adalimumab.¹⁰² After 24 weeks of treatment, the mean change from baseline NAPS I was -15.89 for the ixekizumab group vs -12.53 for the adalimumab group ($p = 0.001$). The IXORA-R trial compared the efficacy of ixekizumab to guselkumab in the treatment of nail psoriasis.¹⁰⁴ From weeks 12 to 24, patients either received ixekizumab 80 mg Q4W or guselkumab 100 mg at weeks 12 and 20. The results showed that ixekizumab was superior in efficacy in the treatment of NP at week 24, as more patients treated with ixekizumab achieved a Physician's Global Assessment of Fingernail Psoriasis (f-PGA) of 0/1 (75 vs 54%; $p = 0.020$).

Egeberg et al conducted a post-hoc analysis to assess improvements in NP among patients from the long-term extension of the UNCOVER-3 study who received ixekizumab and had either any degree of NP (NAPS I > 1) or significant NP (fingernail NAPS I ≥ 16 and ≥ 4 fingernails involved) at baseline.¹⁰⁵ Efficacy outcomes reported through week 264 included the mean percentage improvements from baseline in NAPS I score and the proportion of patients achieving NP resolution (NAPS I = 0). In UNCOVER-3, 56.9% (219/385) of patients had NP at baseline; of those, 61.2% (134/219) had significant NP. At week 60, a total of 66.9% and 59.1% of patients with baseline nail psoriasis and significant baseline nail psoriasis, respectively, reported complete clearance of NP, an effect which was sustained through week 264. In another study, Elewski et al analysed simultaneous skin and nail clearance in patients with psoriasis across five head-to-head trials comparing ixekizumab with other biologics.¹⁰⁶ Data were assessed in patients with moderate-to-severe psoriasis (with or without PsA) with nail psoriasis at baseline from the IXORA-R, IXORA-S, UNCOVER-2, UNCOVER-3, and SPIRIT-H2H trials.^{99–104} Ixekizumab achieved significantly greater simultaneous skin and nail complete clearance than etanercept (UNCOVER-2: $p < 0.001$ and UNCOVER-3: $p < 0.001$) at week 12, demonstrating an efficacious and rapid response. Across all five head-to-head trials, ixekizumab achieved a high rate of simultaneous skin and nail clearance (range: 28.6–45.9% of patients) by week 24 that was maintained up to week 52 (range: 40.5–51.4% of patients). Ixekizumab achieved numerically greater simultaneous complete clearance than guselkumab at week 24 ($p = 0.079$), but statistically significant greater simultaneous clearance compared to ustekinumab ($p < 0.001$) and adalimumab ($p = 0.006$) at week 24 and week 52 ($p < 0.001$ and $p = 0.007$, respectively). In five head-to-head trials, patients treated with ixekizumab had higher rates of simultaneous complete skin and nail clearance compared to etanercept, guselkumab, ustekinumab, and adalimumab.

Ixekizumab also proved to be effective in treating NP in a case of a patient who had discontinued secukinumab due to secondary inefficacy.¹⁰⁷ Barisic et al reported the case of a patient with all six domains of psoriatic PsA (psoriasis, peripheral arthritis, axial skeletal manifestations, dactylitis, nail changes, and enthesitis) unresponsive to conventional synthetic DMARDs, NSAIDs, and steroids, as well as topical treatments and phototherapy. After starting golimumab therapy, the patient had achieved partial remission. After 24 months, treatment was switched to secukinumab because of secondary ineffectiveness. The skin, nail and joint manifestations relapsed after 21 months of therapy. The patient was then cycled to ixekizumab with an excellent result. The authors suggested that IL-17A inhibitor cycling may be a successful treatment option in some difficult to treat PsA patients.¹⁰⁷

Secukinumab

Secukinumab is a human monoclonal antibody that selectively targets and neutralizes interleukin (IL)-17A, approved for the treatment of moderate-to-severe psoriasis and PsA [COSENTIX]. Secukinumab.¹⁰⁸

Pistone et al reported the case of fifteen patients with moderate-severe plaque psoriasis and NP treated with secukinumab.¹⁰⁹ At baseline, mean NAPS I was 69.87 ± 32.51 , median 66. After 6 weeks of treatment with secukinumab 300 mg mean NAPS I was reduced by 50%. At week 6, subungual hyperkeratosis and onycholysis were reduced. At week 12, salmon spots and leukonychia were not present; subungual hyperkeratosis, onycholysis and Beau's lines were present only in 3% of patients. Pitting frequency was reduced to almost 15%. At week 12, NAPS I reduction was by 80%. Improvement of nail involvement was slower than improvement of skin lesions, but nail disease mean index was reduced

almost at the level of skin indexes after 12 weeks of treatment. In 2020, the TRANSFIGURE trial demonstrated sustained efficacy of secukinumab in the treatment of NP.^{110,111} Patients received placebo or secukinumab 150 mg or 300 mg weekly for 5 weeks followed by every 4 weeks. Placebo patients were re-randomized to 150 mg or 300 mg secukinumab and patients were followed up to 2.5 years. Mean NAPS I improvement was evaluated at weeks 16, 32, and 2.5 years. Both dosages of secukinumab demonstrated superiority to placebo at week 16 [37.9 and 45.3 vs 10.8 (placebo); <0.001], and efficacy was maintained at week 32 (52.6 and 63.6, respectively) and at 2.5 years (63.6 and 73.3, respectively).

A post-hoc analysis of the results from the phase 3 FUTURE 5 study evaluated the impact of secukinumab on NP in patients with PsA with concomitant NP.¹¹² Patients were randomly allocated to receive subcutaneous secukinumab (300 mg load [300 mg], 150 mg load [150 mg], and 150 mg [no load]) or placebo weekly and then every 4 weeks starting Week 4. Key assessments through Week 104 included mNAPS I. At baseline, 66.6% patients (663/996) had concomitant NP. Secukinumab reduced mNAPS I score at Week 16 versus placebo: -8.71 (300 mg), -8.95 (150 mg), -7.55 (150 mg no load) versus -2.34 (placebo); all $p < 0.0001$. Overall, the improvements reported at Week 16 sustained through Week 104.

In isolated NP, secukinumab has also been administered by intramatrix injection.¹¹³

He et al recruited 6 patients with psoriasis vulgaris and nail psoriasis. The number of involved fingernails was 9.2 ± 1.3 . All the patients did not receive systemic treatment including immunosuppressors and biologics in the previous 3 months. After local anaesthesia, 3 nails of left hand were treated with intramatrix injections of secukinumab in different concentrations, 7.5 mg/mL, 15 mg/mL and 30mg/mL, respectively. The original 150 mg/mL secukinumab was diluted with sterile water for injection. The needle was inserted from the two sides of the proximal nail fold. The injection volume of each side was 0.05 mL every time. All patients received 5–6 times treatments every 2 weeks. All enrolled nails were assessed with NAPS I score from baseline to week 12 fortnightly. After the last treatment, patients were followed up until week 24. The untreated symmetrical finger of right hand was considered as a control group. At week 24, the mean improvement rate of NAPS I was 73.2% and 18.3%, respectively ($p < 0.01$) between the treated nails and the control. The mean improvement rate of NAPS I was 76.1%, 66.1% and 75.7% for secukinumab concentration of 7.5 mg/mL, 15 mg/mL and 30 mg/mL, respectively, and there was no significant efficacy difference among three concentrations. At week 24, the mean improvement rate of NAPS I of all the treated nails was 88.7% and 63.1% for nail bed and nail matrix respectively ($p < 0.05$). Among 3 types of concentrations, the overall effect on nail bed was better than nail matrix. The low-dose intramatrix injection did not have significant effect on skin lesions. No side effects were detected, apart from injection pain. The accumulation of secukinumab locally may have resulted in sustained nail improvement of the untreated 12 weeks.

Brodalumab

Brodalumab is a human anti-interleukin-17 receptor A (IL-17RA) monoclonal antibody available for use in patients with moderate to severe plaque psoriasis.¹³⁸

In 2020, a post-hoc analysis of two-phase III studies (AMAGINE-2/-3) assessed the treatment efficacy of brodalumab in NP.¹³⁹ Patients received brodalumab 210 mg Q2W or ustekinumab every 12 weeks through 52 weeks with baseline NAPS I of ≥ 6 . Nail clearance efficacy was measured by improvement in mean NAPS I (range 0–32), percentage of responders with a NAPS I of 0, and percent improvement rates from baseline NAPS I.

Endpoints included mean NAPS I improvement and achievement of a NAPS I 0 score (absence of all parameters in the NAPS I). Comparison of brodalumab and ustekinumab demonstrated an improved mean NAPS I score for brodalumab: 43.7 versus 31.8 (week 12), 76.9 versus 58.9 (week 24), 82.4 versus 69 (week 36), and 83.1 versus 75 (week 52); significance ($p < 0.05$) was cited for all comparisons with the exception of week 52. Achievement of NAPS I 0 was the following for brodalumab compared to ustekinumab: 7.9 versus 2.2 (week 12), 31.6 versus 18.8 (week 24), 54.2 versus 33.7 (week 36), and 63.8 versus 39.1 (week 52); significance ($p < 0.05$) was obtained for all comparisons. At week 52, observed mean percent improvement rate from baseline NAPS I was 83.1% in patients treated with brodalumab versus 75% in patients treated with ustekinumab.

In an open-label, single-center study in 30 patients with NP, brodalumab at a dose of 210mg at baseline, weeks 1, 2 and 3 and every two weeks thereafter demonstrated statistically significant reductions in NAPS I for fingers and toes at

weeks 12 and 24 compared with baseline ($p < 0.001$). At baseline mean NAPSI score was 44.5. At week 12, mean NAPSI score of fingernails was 9.6 and at week 24 was 2.63; meanwhile at week 12 mean NAPSI score of toenails was 16.1 and at week 24 was 7.2. In a subanalysis of a Phase 2, randomized trial, 12 weeks of treatment with brodalumab 210 mg Q2W versus placebo resulted in a mean NAPSI improvement of 47.6% (35.2%) versus 9.6% (86.2%), respectively.¹¹⁴ In a real-world case series, four patients with psoriatic nail involvement achieved significant or complete clearance with brodalumab after 12–20 weeks of treatment.¹⁴⁰ Improvements in QOL were also reported, with all four patients achieving PASI of ≤ 1.9 and DLQI of ≤ 1 by week 44.

Bimekizumab

Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F and IL-17A recently approved for the treatment of moderate-to-severe psoriasis.¹⁴¹

Merola et al compared the efficacy and safety of bimekizumab with placebo over 16 weeks in patients with active PsA and previous inadequate response or intolerance to TNF α inhibitors.¹¹⁵ A total of 556 patients were screened and 400 patients were randomly assigned to bimekizumab 160 mg every 4 weeks ($n = 267$) or placebo ($n = 133$). Among patients with mNAPSI greater than 0 at baseline, at week 16 mNAPSI 0 was achieved by 46% of patients treated with bimekizumab versus 14% of patients taking placebo.

Interleukin-23 Inhibitors

Guselkumab

Guselkumab is a monoclonal antibody that acts by inhibiting IL-23 p19 subunit without binding to IL-12 and it is approved for the treatment of moderate-to-severe psoriasis and PsA.¹⁴² In 2018, Foley et al compared the efficacy data of guselkumab with adalimumab and placebo from the VOYAGE 1 and 2 trials for psoriasis in specific body regions, including the nails.¹⁴³ These were double-blind, placebo-controlled trials assessing the efficacy of guselkumab versus adalimumab. F-PGA and NAPSI were included endpoints. Fingernail involvement with psoriasis was evaluated using NAPSI and f-PGA, a 5-point scale, with 0 indicating clear and 4 indicating severe nail involvement.

Of the 1829 randomized patients, 1049 (57.4%) had fingernail psoriasis at baseline. Among these patients, 928 (50.7%) had a score of 2 or higher on the f-PGA at baseline.

At week 16, the percentage of patients achieving cleared or minimal fingernail psoriasis (f-PGA score of 0 or 1) was superior in the guselkumab group compared to the placebo group (46.7 vs 15.2%; $p < 0.001$). The f-PGA responses were comparable in guselkumab- and adalimumab-treated patients at week 24 (252 [60.0%] vs 191 [64.3%], $p = .11$). A statistically significantly higher number of guselkumab-treated patients achieved f-PGA score of 0 compared with placebo at week 16 (52 [12.4%] vs 8 [3.8%], $p < .001$), whereas comparable proportions of guselkumab- and adalimumab-treated patients achieved f-PGA scores of 0 at week 24 (115 [27.4%] vs 83 [27.9%], $p = .63$). Likewise, improvements in NAPSI score were statistically significantly greater for the guselkumab group vs the placebo group at week 16 (mean improvement, 37.5% vs 0.7%; $p < .001$) and comparable between the guselkumab and adalimumab groups at week 24 (52.9% vs 51.2%, $p = .96$).

Ohtsuki et al compared guselkumab with placebo in 192 patients.¹¹⁶ Among patients with NP ($n = 126$), a significant decrease in mNAPSI score (0–8) of -1.2 and -1.5 was observed for the guselkumab 50 and 100 mg groups, compared with -0.2 for the placebo group, at week 16. A 52-week real-life single-center retrospective study was performed to evaluate the long-term efficacy and safety of guselkumab in patients who previously failed anti-IL17.¹⁴⁴ A total of 44 patients were enrolled. Mean NAPSI score (SD) decreased from 2.9 ± 6.2 at baseline to 0.9 ± 1.5 at week 28 ($p < 0.05$). Megna et al conducted a real-life retrospective observational study enrolling moderate-to-severe psoriasis patients to compare the efficacy and safety in real life of guselkumab, tildrakizumab and risankizumab, particularly focusing on difficult to treat areas. The study showed no significant differences in terms of NAPSI response between the 3 anti-IL-23 biologics with percentage reduction of 79.4%, 82.6% and 75% at week 16 for guselkumab, risankizumab and tildrakizumab, respectively.¹⁴⁵

A prospective, non-interventional, multicentre study evaluated the efficacy and safety of guselkumab in patients with moderate-to-severe psoriasis who received 52 weeks of treatment. NAPSI score was included among the secondary

endpoints. Among the 303 patients enrolled, 297 had a baseline NAPSI ≥ 1 . Mean NAPSI score was 4.2 at baseline and decreased to 1.2 at W52, with a percentage mean change of -71.4% . Similarly, the mean number of affected nails was 6.8 at baseline, which decreased to 3.3 at W28 and to 2.3 at W52.¹¹⁷

Risankizumab

Risankizumab is a humanized monoclonal IgG1 antibody that selectively targets the special human IL-23 p19 subunit.¹⁴⁶ In February 2019, Risankizumab was approved for the treatment of moderate to severe psoriasis as well as PsA.^{147,148} The efficacy and safety of risankizumab was evaluated in the randomised, placebo-controlled, double-blind KEEPsAKE 1 trial.^{118,149} A total of 964 patients with active PsA was randomised (1:1) to receive risankizumab 150 mg or placebo at weeks 0, 4 and 16. The primary endpoint was the proportion of patients achieving $\geq 20\%$ improvement in American College of Rheumatology criteria (ACR20) at week 24. Secondary endpoints included change from baseline in mNAPSI and change from baseline in f-PGA, based on the worse of nail bed or nail matrix signs of disease severity 0 (clear) to 4 (severe). Risankizumab treatment resulted in significant improvements from baseline in NP (mNAPSI and f-PGA) among patients with psoriatic nail disease at baseline. At baseline, mean mNAPSI was 18.1 and mean F-PGA was 2.1. At week 24 mean mNAPSI decreased to 9.8 meanwhile mean PGA-F became 0.8.

Moreover, a 52-week real-life retrospective study was performed to assess the long-term efficacy and safety of risankizumab in patients who previously failed anti-IL17.¹¹⁹ A total of 39 patients were enrolled. Fifteen (38.5%) patients were also affected by PsA and nail involvement was observed in nine subjects (23.1%). PASI, BSA and NAPSI were assessed at each follow-up visit (week 4, week 16, week 28, week 40, week 52). At baseline, mean NAPSI (SD) was 9.3 ± 4.7 . NAPSI clinical improvement was already assessed at week 4 (6.7 ± 4.6), being statistically significant for the first time at week 16 (4.1 ± 2.4 , $p < 0.01$) and then up to week 52 (1.4 ± 0.8 , $p < 0.0001$). Alajlan et al described the case of a patient who suffered from NP with no skin or joint involvement who developed a paradoxical cutaneous psoriatic lesions after the administration of adalimumab 40 mg every 2 weeks, with minimal improvement of NP after 9 months of treatment.¹⁵⁰ He was then switched to risankizumab 150 mg (at week 0, week 4 and every 12 weeks thereafter). Significant improvement was noted at 12 weeks of risankizumab therapy, where the patient reported 70% subjective improvement of the affected fingernails, with no new involvement of previously unaffected nails, and clearance of skin psoriasis.

Tildrakizumab

Tildrakizumab is a humanised monoclonal antibody that selectively targets the p19 subunit of IL-23 approved for the treatment of moderate-to-severe chronic plaque psoriasis.^{151–153} The reSURFACE 1 and reSURFACE 2 clinical trials evaluated the long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis through 148 weeks.¹⁵⁴ NAPSI was not captured in these trials. In terms of evidence to date evaluating the use of tildrakizumab, there are no RCTs evaluating its efficacy in nail disease, although some real-life experiences suggest that tildrakizumab may be a valid treatment option. Ismail et al reported the case of a man with psoriatic nail dystrophy and PsA with an excellent clinical response both on nail disease and arthritis.¹²⁰ Simpson et al reported two cases of treatment resistant NP which showed marked improvement with the use of tildrakizumab.¹⁵⁵ The dosing regimen utilized was consistent with that used to treat chronic plaque psoriasis, with 100 mg subcutaneously at Day 0 and Week 4, and maintenance dosing of 100 mg every 12 weeks thereafter. One patient was commenced on tildrakizumab for a 5-year history of treatment resistant NP predominantly affecting the toenails, with no history of plaque psoriasis elsewhere on the body and no history of PsA. At baseline mNAPSI was 44. After 6 months of treatment with tildrakizumab, mNAPSI score reduced to 13. After 12 months of treatment, total mNAPSI further decreased to score of 8, resulting in a reduction in scoring of 81.8% from baseline. The other patient started tildrakizumab for a psoriasis affecting the nails and scalp, resistant to MTX and cyclosporine. The patient had concomitant PsA. Baseline mNAPSI score was 56 and DLQI was 19. At the 6-month follow-up, NAPSI had improved with a reduction of more than 75% from baseline, to a score of 12. At the 12-month follow-up, the patient's nail psoriasis continued to improve with NAPSI of 7. The patient has not developed any adverse event. Galluzzo et al conducted a 28-week retrospective study on 18 patients to evaluate the effectiveness of tildrakizumab in difficult sites.¹²¹ Safety and efficacy were assessed at weeks 0, 4, 12 and 28 using the PASI, static Physician's Global Assessment of Genitalia (sPGA-G), Psoriasis Scalp Severity Index (PSSI), NAPSI and the Palmoplantar Psoriasis

Area and Severity Index (ppPASI). The NAPSI score for nail involvement decreased to a lesser extent compared to other outcome measures but was decreased by 29.3% at week 12 (from 48.4 to 34.2) and by 67.6% at week 28 (from 48.4 to 15.7), corroborating results from these other real-life experiences and confirming that tildrakizumab could be an effective therapeutic choice for the treatment of this difficult site. Brunasso et al conducted a retrospective study of patients affected by plaque psoriasis who underwent tildrakizumab therapy to describe and compare the response of the NP and the plaque psoriasis elsewhere in the body.¹²² Eight patients treated with tildrakizumab affected by psoriasis (mean baseline PASI score 13) with nail involvement (mean baseline mNAPSI score 51.9), were followed for at least 20 weeks. At week 4, the mean PASI was 6.6 (49% improvement), and the mean mNAPSI was 30.8 (40.6% improvement). At week 20, the mean PASI was 2.1 (84% improvement), and the mean mNAPSI was 5.1 (90% improvement).

Discussion

Nails are frequently involved in patients with psoriasis. NP is seen in up to 80% of patients with psoriasis and may be the only disease manifestation in 6% of cases.^{156–164} Nail involvement can be a negative prognostic factor correlated with more severe disease, and, most importantly, characterized by earlier onset and a higher risk of PsA. Accordingly, it can also result in significant functional impairment and reduced QoL.¹⁵⁶ Hence, NP deserve a prompt and adequate treatment. Several topical and systemic drugs have been studied for this condition. Recommendations provided by an expert group consensus were previously published.¹²⁵ Topical and injectable therapies are recommended for few-nail disease (≤ 3 nails involved). Systemic therapies, including biologics, can be considered for patients with multiple and resistant nail disease, impaired QoL, and severe skin and joint involvement.¹²⁵ Topical therapies that can be considered include calcipotriol and glucocorticoid preparations, topical tacrolimus, topical cyclosporine and intralesional glucocorticoids. Considering the reported efficacy of intralesional MTX in recent studies, this treatment also may be considered among first-line treatments. In cases of nail matrix involvement only, first-line therapy should be corticosteroids or intralesional MTX, whereas in cases of exclusive nail bed involvement topical corticosteroids or vitamin D/corticosteroid combinations are preferred.¹²⁵ Systemic therapies should be considered when the disorder involves more than 3 nails, has extensive skin and joint involvement, and has a significant impact on QoL, due to their best long-term efficacy.¹²⁵ In detail, conventional and biologic systemic drugs demonstrated efficacy in recent trials, including acitretin, MTX, cyclosporine, apremilast, adalimumab, infliximab, etanercept, certolizumab, golimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab and tildrakizumab. More recently, the Group for Research and Assessment of PsO and PsA (GRAPPA) included NP as one of the 6 key domains of PsA (peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease).¹⁶⁴ For the treatment of patients with moderate-to-severe NP, the 2021 GRAPPA treatment guidelines recommended biologic therapy given the rigorous evidence from clinical trials. Although more studies are needed, head-to-head studies have been conducted among biologic drugs showing that some biologics may be more effective than others in treating NP.

Brodalumab demonstrated to be more effective than ustekinumab at weeks 12, 24, 36, and 52.¹³⁹ IL-17 inhibitors have faster onset of action than TNF-alpha inhibitors but have similar long-term efficacy, as demonstrated by ixekizumab, which provided significantly greater improvement in NP as early as Week 12 compared to placebo or etanercept.¹⁰¹

Other head-to-head trials of patients with NP revealed a significantly greater response in terms of NAPSI score reduction with ixekizumab vs ustekinumab at week 16.¹⁰⁰ Ixekizumab was also shown to be more effective than guselkumab at week 24.¹⁰⁴ Another study highlighted that some IL-23 inhibitors have similar efficacy to TNF-alpha inhibitors: guselkumab and adalimumab displayed similar efficacy results at week 24.¹⁴³ Moreover, nail involvement could be considered as a predictor of differential treatment effects.⁹¹ In a recent study, ustekinumab gave a better response in terms of PASI reduction in patients without nail involvement than in patients with NP. This difference was not found in patients treated with secukinumab in which similar percentages of patients with and without nail involvement went through PASI reduction.

These data are in line with those presented in a recent meta-analysis conducted to indirectly compare the efficacy of six biologics in achieving complete resolution of NP at week 24–26 in patients with moderate-to-severe psoriasis and concomitant NP.¹⁶⁵ The outcomes were the proportion of psoriasis patients and concomitant NP defined as NAPSI 1, mNAPSI 1, or PGA-F 1 that achieved complete resolution of NP (NAPSI = 0, mNAPSI = 0, PGA-F = 0) at week 24–26.

The probabilities of achieving complete resolution of NP at week 24–26 were 46.5% (95% CrI 35.1–58.0) for ixekizumab, 37.0% (95% CrI 17.0–61.0) for brodalumab, and 28.3% (95% CrI 24.4–32.4), 27.7% (95% CrI 21.1–35.1), 20.8% (95% CrI 10.2–35.2), and 0.8% (95% CrI 0.0–8.9) for adalimumab, guselkumab, ustekinumab, and infliximab, respectively.

The percentage of patients achieving complete nail resolution was numerically higher with ixekizumab than with all comparators, followed by brodalumab. Results from this study confirm that biologics approved for the treatment of psoriasis are efficacious in achieving complete resolution of NP after 24–26 weeks in comparison with placebo.¹⁶⁶

However, a limitation in the analysis of these studies is the lack of unambiguous parameters in the assessment of NP improvement. Some studies, especially case reports and case series, sometimes lack the use of scores but report only clinical descriptions of improvement of nail lesions. The presence of different time frames in the assessment of NP changes is another limitation in the evaluation of studies.

Conclusion

In conclusion, NP deserves a prompt and adequate treatment. Certainly, when nail involvement is more extensive, systemic medications are preferred.^{158,159} When NP is associated with psoriatic arthritis the drugs of first choice are those that are also active on the joint component. Among the systemic drugs, ixekizumab appears to be the one with more studies of superiority over other biologic drugs in the treatment of NP, followed by adalimumab. Several therapies have demonstrated efficacy and safety in the treatment of NP; however, the choice of treatment depends not only on the severity of the nail involvement, but also on whether PsA is present, the patient's comorbidities other than PsA, previous treatment history, and the patient's drug preferences. More data and dedicated head-to-head trials in NP are needed in order to establish an evidence-based treatment algorithm.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol*. 2014;70:512–516. doi:10.1016/j.jaad.2013.11.013
2. Langley RG, Daudén E. Treatment and management of psoriasis with nail involvement: a focus on biologic therapy. *Dermatology*. 2010;221(Suppl 1):29–42. doi:10.1159/000316179
3. Ortonne JP, Baran R, Corvest M, Schmitt C, Voisard JJ, Taieb C. Development and validation of nail psoriasis quality of life scale (NPQ10). *J Eur Acad Dermatol Venereol*. 2010;24:22–27. doi:10.1111/j.1468-3083.2009.03344.x
4. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol*. 1999;41(3 Pt 1):401–407. doi:10.1016/S0190-9622(99)70112-X
5. Augustin M, Reich K, Blome C, Schafer I, Laass A, Radtke MA. Nail psoriasis in Germany: epidemiology and burden of disease. *Br J Dermatol*. 2010;163(3):580–585. doi:10.1111/j.1365-2133.2010.09831.x
6. Jiaravuthisan MM, Sasseville D, Vender RB, Murphy F, Muhn CY. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. *J Am Acad Dermatol*. 2007;57(1):1–27. doi:10.1016/j.jaad.2005.07.073
7. Pasch MC. Nail psoriasis: a review of treatment options. *Drugs*. 2016;76(6):675–705. doi:10.1007/s40265-016-0564-5
8. de Berker D. Management of nail psoriasis. *Clin Exp Dermatol*. 2000;25:357–362. doi:10.1046/j.1365-2230.2000.00663.x
9. McGonagle D, Ash Z, Dickie L, McDermott M, Aydin SZ. The early phase of psoriatic arthritis. *Ann Rheum Dis*. 2011;70(Suppl 1):i71–6. doi:10.1136/ard.2010.144097
10. McGonagle D, Tan AL, Benjamin M. The nail as a musculoskeletal appendage-implications for an improved understanding of the link between psoriasis and arthritis. *Dermatology*. 2009;218(2):97–102. doi:10.1159/000182250
11. Sobolewski P, Walecka I, Dopytalska K. Nail involvement in psoriatic arthritis. *Reumatologia*. 2017;55(3):131–135. doi:10.5114/reum.2017.68912

12. Klaassen KM, van de Kerkhof PC, Pasch MC. Nail psoriasis: a questionnaire-based survey. *Br J Dermatol*. 2013;169(2):314–319. doi:10.1111/bjd.12354
13. Dogra S, Yadav S. Acitretin in psoriasis: an evolving scenario. *Int J Dermatol*. 2014;53(5):525–538. doi:10.1111/ijd.12365
14. Brazzelli V, Martinoli S, Prestinari F, Borroni G. An impressive therapeutic result of nail psoriasis to Acitretin. *J Eur Acad Dermatol Venereol*. 2004;18(2):229–230. doi:10.1111/j.1468-3083.2004.00667.x
15. Brazzelli V, Martinoli S, Prestinari F, Borroni G. Severe nail psoriasis with a rapid response to Acitretin. *Clin Exp Dermatol*. 2009;34(7):e332–e333. doi:10.1111/j.1365-2230.2009.03282.x
16. Tosti A, Ricotti C, Romanelli P, Cameli N, Piraccini BM. Evaluation of the efficacy of Acitretin therapy for nail psoriasis. *Arch Dermatol*. 2009;145(3):269–271. doi:10.1001/archdermatol.2008.600
17. Ricceri F, Pescitelli L, Tripo L, Bassi A, Prignano F. Treatment of severe nail psoriasis with Acitretin: an impressive therapeutic result. *Dermatol Ther*. 2013;26(1):77–78. doi:10.1111/j.1529-8019.2012.01539.x
18. Krajewska-Włodarczyk M, Żuber Z, Owczarczyk-Saczonek A. Ultrasound evaluation of the effectiveness of the use of acitretin in the treatment of nail psoriasis. *J Clin Med*. 2021;10(10):2122. doi:10.3390/jcm10102122
19. Graceffa D, Bonifati C, Pacifico A, Morrone A. When the old works better than the new: a case of severe nail psoriasis successfully treated with Acitretin after failure of two biologic regimens. *Dermatol Ther*. 2020;33(4):e13615. doi:10.1111/dth.13615
20. Mukai MM, Poffo IF, Werner B, Brenner FM, Lima Filho JH. NAPSUI utilization as an evaluation method of nail psoriasis in patients using Acitretin. *An Bras Dermatol*. 2012;87(2):256–262. doi:10.1590/S0365-05962012000200010
21. Kuhn A, Ruland V, Patsinakidis N, Luger TA. Use of methotrexate in patients with psoriasis. *Clin Exp Rheumatol*. 2010;28(5 Suppl 61):S138–S144.
22. Gümüşel M, Özdemir M, Mevlitoğlu I, Bodur S. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one-blind, randomized study. *J Eur Acad Dermatol Venereol*. 2011;25(9):1080–1084. doi:10.1111/j.1468-3083.2010.03927.x
23. Tsiskarishvili NV, Katsitadze AG, Tsiskarishvili NI. Assessment of psoriatic nail lesions therapy by means of nail psoriasis severity index. *Georgian Med News*. 2011;199:43–47.
24. Demirsoy EO, Kıran R, Salman S, et al. Effectiveness of systemic treatment agents on psoriatic nails: a comparative study. *J Drugs Dermatol*. 2013;12(9):1039–1043.
25. Coates LC, Helliwell PS. Methotrexate efficacy in the tight control in psoriatic arthritis study. *J Rheumatol*. 2016;43(2):356–361. doi:10.3899/jrheum.150614
26. Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. *Arthritis Rheumatol*. 2019;71(7):1112–1124. doi:10.1002/art.40851
27. Warren RB, Mrowietz U, von Kiedrowski R, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10068):528–537. doi:10.1016/S0140-6736(16)3127-4
28. Drach M, Papageorgiou K, Maul JT, et al. Effectiveness of methotrexate in moderate to severe psoriasis patients: real-world registry data from the Swiss Dermatology Network for Targeted Therapies (SDNTT). *Arch Dermatol Res*. 2019;311(10):753–760. doi:10.1007/s00403-019-01945-6
29. Lee JY. Severe 20-nail psoriasis successfully treated by low dose methotrexate. *Dermatol Online J*. 2009;15(11):8.
30. Soleymani T, Vasantachart JM, Wu JJ. Comparison of guidelines for the use of cyclosporine for psoriasis: a critical appraisal and comprehensive review. *J Drugs Dermatol*. 2016;15(3):293–301.
31. Feliciani C, Zampetti A, Forleo P, et al. Nail psoriasis: combined therapy with systemic cyclosporin and topical calcipotriol. *J Cutan Med Surg*. 2004;8(2):122–125. doi:10.1177/120347540400800208
32. Karanikolas GN, Koukli EM, Katsalira A, et al. Adalimumab or cyclosporine as monotherapy and in combination in severe psoriatic arthritis: results from a prospective 12-month nonrandomized unblinded clinical trial. *J Rheumatol*. 2011;38(11):2466–2474. doi:10.3899/jrheum.110242
33. Sánchez-Regaña M, Sola-Ortigosa J, Alsina-Gibert M, Vidal-Fernández M, Umbert-Millet P. Nail psoriasis: a retrospective study on the effectiveness of systemic treatments (classical and biological therapy). *J Eur Acad Dermatol Venereol*. 2011;25(5):579–586. doi:10.1111/j.1468-3083.2010.03938.x
34. Balak DM. Fumaric acid esters in the management of psoriasis. *Psoriasis Targets Ther*. 2015;5:9–23. doi:10.2147/PTT.S51490
35. Augustin M, Landeck L, Diemert S, et al. Long-term treatment with dimethyl fumarate for plaque psoriasis in routine practice: good overall effectiveness and positive effect on impactful areas. *Dermatol Ther*. 2022;12(5):1121–1131. doi:10.1007/s13555-022-00714-0
36. Vlachou C, Berth-Jones J. Nail psoriasis improvement in a patient treated with fumaric acid esters. *J Dermatolog Treat*. 2007;18(3):175–177. doi:10.1080/09546630701264331
37. Marx JL, Scher RK. Response of psoriatic nails to oral photochemotherapy. *Arch Dermatol*. 1980;116:1023–1024. doi:10.1001/archderm.1980.01640330061013
38. Handfield-Jones SE, Boyle J, Harman RR. Local PUVA treatment for nail psoriasis. *Br J Dermatol*. 1987;116:280–281. doi:10.1111/j.1365-2133.1987.tb05834.x
39. Stern DK, Creasey AA, Quijije J, et al. UV-A and UV-B penetration of normal human cadaveric fingernail plate. *Arch Dermatol*. 2011;147(4):439–441. doi:10.1001/archdermatol.2010.375
40. Rich P, Gooderham M, Bachelez H, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *J Am Acad Dermatol*. 2016;74(1):134–142. doi:10.1016/j.jaad.2015.09.001
41. Reich K, Gooderham M, Bewley A, et al. Safety and efficacy of apremilast through 104 weeks in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: findings from the LIBERATE study. *J Eur Acad Dermatol Venereol*. 2018;32(3):397–402. doi:10.1111/jdv.14738
42. Oak ASW, Ho-Pham H, Elewski BE. Improvement of 11 patients with nail psoriasis with apremilast: results of an investigator-initiated open-label study. *J Am Acad Dermatol*. 2020;83(6):1830–1832. doi:10.1016/j.jaad.2020.05.087
43. Muñoz-Santos C, Sola-Ortigosa J, Vidal D, Guilabert A. Apremilast improves quality of life and ultrasonography parameters in patients with nail psoriasis: a prospective cohort study. *J Dermatol*. 2021;48(10):1593–1596. doi:10.1111/1346-8138.16074

44. Magdaleno-Tapia J, Valenzuela-Oñate C, Ortiz-Salvador JM, Subiabre-Ferrer D, Hernández-Bel P. Effective treatment of nail psoriasis with apremilast: report of two cases and review of the literature. *Dermatol Online J*. 2018;24(9):13030/qt27x34947.
45. Ortonne JP, Paul C, Berardesca E, et al. A 24-week randomized clinical trial investigating the efficacy and safety of two doses of etanercept in nail psoriasis. *Br J Dermatol*. 2013;168(5):1080–1087.
46. ENBREL. Etanercept (ENBREL) - Prescribing information; 1998. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s503lbl.pdf. Accessed July 10, 2023.
47. Luger TA, Barker J, Lambert J, et al. Sustained improvement in joint pain and nail symptoms with etanercept therapy in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol*. 2009;23(8):896–904. doi:10.1111/j.1468-3083.2009.03211.x
48. Rallis E, Stavropoulou E, Rigopoulos D, et al. Rapid response of nail psoriasis to etanercept. *J Rheumatol*. 2008;35:544–545.
49. Barrera MV, Habicheyn S, Mendiola MV, et al. Etanercept in the treatment and retreatment of psoriasis in daily clinical practice. *Eur J Dermatol*. 2008;18(6):683–687. doi:10.1684/ejd.2008.0541
50. Coelho JD, Diamantino F, Lestre S, et al. Treatment of severe nail psoriasis with etanercept. *Indian J Dermatol Venereol Leprol*. 2011;77(1):72–74. doi:10.4103/0378-6323.74996
51. Gomez VM, Navarra AR. Marked improvement in nail psoriasis during treatment with etanercept. *Dermatol Ther*. 2011;24(5):498–500. doi:10.1111/j.1529-8019.2012.01472.x
52. Niebel D, Wilsmann-Theis D, Wenzel J. Successful treatment of psoriatic arthritis and comorbid annular atrophic lichen planus with etanercept. *J Dermatol*. 2020;47(4):397–401. doi:10.1111/1346-8138.15222
53. Winterfield LS, Menter A. Infliximab. *Dermatol Ther*. 2004;17(5):409–426. doi:10.1111/j.1396-0296.2004.04044.x
54. Bianchi L, Bergamin A, de Felice C, et al. Remission and time of resolution of nail psoriasis during infliximab therapy. *J Am Acad Dermatol*. 2005;52(4):736–737. doi:10.1016/j.jaad.2004.09.012
55. Fabroni C, Gori A, Troiano M, et al. Infliximab efficacy in nail psoriasis. A retrospective study in 48 patients. *J Eur Acad Dermatol Venereol*. 2011;25(5):549–553. doi:10.1111/j.1468-3083.2010.03826.x
56. Rigopoulos D, Gregoriou S, Stratigos A, et al. Evaluation of the efficacy and safety of infliximab on psoriatic nails: an unblinded, nonrandomized, open-label study. *Br J Dermatol*. 2008;159:453–456. doi:10.1111/j.1365-2133.2008.08686.x
57. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a Phase III, multicentre, double-blind trial. *Lancet*. 2005;366(9494):1367–1374. doi:10.1016/S0140-6736(05)67566-6
58. Saraceno R, Pietroleonardo L, Mazzotta A, Zangrilli A, Bianchi L, Chimenti S. TNF- α antagonists and nail psoriasis: an open, 24-week, prospective cohort study in adult patients with psoriasis. *Expert Opin Biol Ther*. 2013;13(4):469–473. doi:10.1517/14712598.2013.736960
59. Safa G, Darrieux L. Dramatic response of nail psoriasis to infliximab. *Case Rep Med*. 2011;2011:107928. doi:10.1155/2011/107928
60. Hussain W, Coulson I, Owen C. Severe recalcitrant nail psoriasis responding dramatically to infliximab: report of two patients. *Clin Exp Dermatol*. 2008;33:520–522. doi:10.1111/j.1365-2230.2008.02738.x
61. Satoh M, Yamamoto T. Case of recalcitrant nail psoriasis unresponsive to Adalimumab but successfully treated with infliximab. *J Dermatol*. 2017;44(11):e288–e289. doi:10.1111/1346-8138.13947
62. Ruggiero A, Martora F, Picone V, Marano L, Fabbrocini G, Marasca C. Paradoxical hidradenitis suppurativa during biologic therapy, an emerging challenge: a systematic review. *Biomedicine*. 2022;10(2):455. doi:10.3390/biomedicine10020455
63. Irla N, Yawalkar N. Marked improvement in nail psoriasis during treatment with Adalimumab. *Dermatology*. 2009;219(4):353–356. doi:10.1159/000252853
64. Rigopoulos D, Gregoriou S, Lazaridou E, et al. Treatment of nail psoriasis with Adalimumab: an open label unblinded study. *J Eur Acad Dermatol Venereol*. 2010;24(5):530–534. doi:10.1111/j.1468-3083.2009.03453.x
65. Sola-Ortigosa J, Sanchez-Regana M, Umbert-Millet P. Efficacy of Adalimumab in the treatment of psoriasis: a retrospective study of 15 patients in daily practice. *J Dermatolog Treat*. 2012;23(3):203–207. doi:10.3109/09546634.2010.519376
66. Paul C, van de Kerkhof P, Puig L, et al. Influence of psoriatic arthritis on the efficacy of Adalimumab and on the treatment response of other markers of psoriasis burden: subanalysis of the BELIEVE study. *Eur J Dermatol*. 2012;22(6):762–769. doi:10.1684/ejd.2012.1863
67. Thaci D, Unnebrink K, Sundaram M, Sood S, Yamaguchi Y. Adalimumab for the treatment of moderate to severe psoriasis: subanalysis of effects on scalp and nails in the BELIEVE study. *J Eur Acad Dermatol Venereol*. 2015;29(2):353–360. doi:10.1111/jdv.12553
68. Elewski BE, Okun MM, Papp K, et al. Adalimumab for nail psoriasis: efficacy and safety from the first 26 weeks of a phase 3, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2018;78(1):90–9. e1. doi:10.1016/j.jaad.2017.08.029
69. Elewski BE, Baker CS, Crowley JJ, et al. Adalimumab for nail psoriasis: efficacy and safety over 52 weeks from a phase-3, randomized, placebo-controlled trial. *J Eur Acad Dermatol Venereol*. 2019;33(11):2168–2178. doi:10.1111/jdv.15793
70. Leonardi C, Langley RG, Papp K, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. *Arch Dermatol*. 2011;147:429–436. doi:10.1001/archdermatol.2010.384
71. Kokolakis G, Bachmann F, Wolk K, Sabat R, Philipp S. Efficacy of adalimumab for nail psoriasis during 24 months of continuous therapy. *Acta Derm Venereol*. 2020;100(14):adv00214. doi:10.2340/00015555-3545
72. Komatsu-Fujii T, Honda T, Otsuka A, Kabashima K. Improvement of nail lesions in a patient with psoriatic arthritis by switching the treatment from an anti-interleukin-17A antibody to an anti-tumor necrosis factor- α antibody. *J Dermatol*. 2019;46(5):e158–e160. doi:10.1111/1346-8138.14700
73. Komatsu-Fujii T, Honda T, Otsuka A, Kabashima K. Inverse responses of the skin and nail lesions of psoriatic arthritis to an anti-interleukin-17A antibody and an anti-tumor necrosis factor- α antibody. *J Dermatol*. 2019;46(11):e440–e441. doi:10.1111/1346-8138.15006
74. CIMZIA. Certolizumab pegol (CIMZIA) - Prescribing information; 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/cimzia-epar-product-information_en.pdf. Accessed July 10, 2023.
75. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis*. 2014;73(1):48–55. doi:10.1136/annrheumdis-2013-203696
76. Mazzeo M, Dattola A, Cannizzaro MV, Bianchi L. Nail psoriasis treated with certolizumab pegol in patients with psoriatic arthritis: preliminary observation. *Actas Dermosifiliogr*. 2019;110(2):169–171. doi:10.1016/j.ad.2018.02.010

77. Dattola A, Balato A, Megna M, et al. Certolizumab for the treatment of psoriasis and psoriatic arthritis: a real-world multicentre Italian study. *J Eur Acad Dermatol Venereol*. 2020;34(12):2839–2845. doi:10.1111/jdv.16606
78. Umezawa Y, Asahina A, Imafuku S, et al. Efficacy and safety of certolizumab pegol in Japanese patients with moderate to severe plaque psoriasis: 52-week results. *Dermatol Ther*. 2021;11(3):943–960. doi:10.1007/s13555-021-00520-0
79. SIMPONI. Golimumab (SIMPONI) - Prescribing information; 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/simoni-epar-product-information_en.pdf. Accessed July 10, 2023.
80. Mease P, Elaine Husni M, Chakravarty SD, et al. Evaluation of improvement in skin and nail psoriasis in bio-naïve patients with active psoriatic arthritis treated with golimumab: results through week 52 of the GO-VIBRANT study. *ACR Open Rheumatol*. 2020;2(11):640–647. doi:10.1002/acr2.11180
81. Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009;60:976–986. doi:10.1002/art.24403
82. Vieira-Sousa E, Alves P, Rodrigues AM, et al. GO-DACT: a phase 3b randomised, double-blind, placebo-controlled trial of Golimumab plus methotrexate (MTX) versus placebo plus MTX in improving dactylitis in MTX-naïve patients with psoriatic arthritis. *Ann Rheum Dis*. 2020;79:490–498. doi:10.1136/annrheumdis-2019-216500
83. Jung SY. A case of nail psoriasis improved by treatment with golimumab in a psoriatic arthritis patient. *Ann Dermatol*. 2017;29(4):491–492. doi:10.5021/ad.2017.29.4.491
84. Martora F, Megna M, Battista T, et al. Adalimumab, ustekinumab, and secukinumab in the management of hidradenitis suppurativa: a review of the real-life experience. *Clin Cosmet Investig Dermatol*. 2023;16:135–148. doi:10.2147/CCID.S391356
85. Rallis E, Kintzoglou S, Verros C. Ustekinumab for rapid treatment of nail psoriasis. *Arch Dermatol*. 2010;146(11):1315–1316. doi:10.1001/archdermatol.2010.332
86. Rigopoulos D, Gregoriou S, Makris M, et al. Efficacy of ustekinumab in nail psoriasis and improvement in nail-associated quality of life in a population treated with ustekinumab for cutaneous psoriasis: an open prospective unblinded study. *Dermatology*. 2011;223(4):325–329. doi:10.1159/000334482
87. Patsatsi A, Kyriakou A, Sotiriadis D. Ustekinumab in nail psoriasis: an open-label, uncontrolled, 51. nonrandomized study. *J Dermatolog Treat*. 2013;24:96–100. doi:10.3109/09546634.2011.607796
88. Igarashi A, Kato T, Kato M, et al. Efficacy and safety of ustekinumab in 52. Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *J Dermatol*. 2012;39:242–252. doi:10.1111/j.1346-8138.2011.01347.x
89. Youn SW, Kim BR, Cho S, et al. Determination of the nail psoriasis severity index improvement rate standards for nail psoriasis treatment in a Phase IV clinical trial of ustekinumab: the MARCOPOLO study. *J Eur Acad Dermatol Venereol*. 2017;31(6):e298–e299. doi:10.1111/jdv.14083
90. Yang S, Kim BR, Kim M, Youn SW. Toenail Psoriasis during Ustekinumab Therapy: results and Limitations. *Ann Dermatol*. 2021;33(2):131–137. doi:10.5021/ad.2021.33.2.131
91. Conrad C, Ortmann CE, Vandemeulebroecke M, Kasperek T, Reich K. Nail involvement as a predictor of differential treatment effects of secukinumab versus ustekinumab in patients with moderate to severe psoriasis. *Dermatol Ther*. 2022;12(1):233–241. doi:10.1007/s13555-021-00654-1
92. Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-week CLARITY results). *Dermatol Ther*. 2018;8:571–579. doi:10.1007/s13555-018-0265-y
93. Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol*. 2015;73:400–9. doi:10.1016/j.jaad.2015.05.013
94. Vitiello M, Tosti A, Abuchar A, Zaiac M, Kerdel FA. Ustekinumab for the treatment of nail psoriasis in heavily treated psoriatic patients. *Int J Dermatol*. 2013;52(3):358–362. doi:10.1111/j.1365-4632.2011.05320.x
95. Byun SY, Kim BR, Choi JW, Youn SW. Severe nail fold psoriasis extending from nail psoriasis resolved with ustekinumab: suggestion of a cytokine overflow theory in the nail unit. *Ann Dermatol*. 2016;28(1):94–97. doi:10.5021/ad.2016.28.1.94
96. Megna M, Potestio L, Camela E, Fabbrocini G, Ruggiero A. Ixekizumab and brodalumab indirect comparison in the treatment of moderate to severe psoriasis: results from an Italian single-center retrospective study in a real-life setting. *Dermatol Ther*. 2022;35(9):e15667. doi:10.1111/dth.15667
97. Marasca C, Fornaro L, Martora F, Picone V, Fabbrocini G, Megna M. Onset of vitiligo in a psoriasis patient on ixekizumab. *Dermatol Ther*. 2021;34(5):e15102. doi:10.1111/dth.15102
98. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med*. 2012;366:1190–1199. doi:10.1056/NEJMoa1109997
99. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (Adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis*. 2017;76:79–87. doi:10.1136/annrheumdis-2016-209709
100. Wasel N, Thaçi D, French LE, et al. Ixekizumab and ustekinumab efficacy in nail psoriasis in patients with moderate-to-severe psoriasis: 52-week results from a phase 3, head- to-head study (IXORA-S). *Dermatol Ther*. 2020;10:663–670. doi:10.1007/s13555-020-00383-x
101. Leonardi C, Reich K, Foley P, et al. Efficacy and safety of ixekizumab through 5 years in moderate-to-severe psoriasis: long-term results from the UNCOVER-1 and UNCOVER-2 Phase- 3 randomized controlled trials. *Dermatol Ther*. 2020;10:431–447. doi:10.1007/s13555-020-00367-x
102. van de Kerkhof P, Guenther L, Gottlieb AB, et al. Ixekizumab treatment improves fingernail psoriasis in patients with moderate-to-severe psoriasis: results from the randomized, controlled and open-label phases of UNCOVER-3. *J Eur Acad Dermatol Venereol*. 2017;31(3):477–482. doi:10.1111/jdv.14033
103. Mease PJ, Smolen JS, Behrens F, et al. A head-to- head comparison of the efficacy and safety of ixekizumab and Adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann Rheum Dis*. 2020;79(1):123–131.

104. Blauvelt A, Leonardi C, Elewski B, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 24-week efficacy and safety results from a randomized, double-blinded trial. *Br J Dermatol*. 2020;182(6):1348–1358. doi:10.1111/bjd.18851
105. Egeberg A, Kristensen LE, Vender R, et al. Sustained resolution of nail psoriasis through 5 years with ixekizumab: a post-hoc analysis from UNCOVER-3. *Acta Derm Venereol*. 2022;102:adv00787. doi:10.2340/actadv.v102.2269
106. Elewski BE, Blauvelt A, Gallo G, et al. Simultaneous nail and skin clearance in ixekizumab head-to-head trials for moderate-to-severe psoriasis and psoriatic arthritis. *Dermatol Ther*. 2022;12(4):911–920. doi:10.1007/s13555-022-00704-2
107. Barešić M, Smiljanić Tomičević L, Anić B, Mayer M. Successful IL-17A inhibitor cycling in psoriatic arthritis patient: a case report and a literature review. *Rheumatol Int*. 2022;42(2):365–370. doi:10.1007/s00296-021-05065-1
108. COSENTIX. Secukinumab (COSENTIX) - Prescribing information; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125504s0431bl.pdf. Accessed July 10, 2023.
109. Pistone G, Gurreri R, Tilotta G, Castelli E, Bongiorno MR. Secukinumab efficacy in the treatment of nail psoriasis: a case series. *J Dermatolog Treat*. 2018;29(sup1):21–24. doi:10.1080/09546634.2018.1529381
110. Reich K, Sullivan J, Arenberger P, et al. Effect of secukinumab on the clinical activity and disease burden of nail psoriasis: 32-week results from the randomized placebo-controlled TRANSFIGURE trial. *Br J Dermatol*. 2019;181(5):954–966. doi:10.1111/bjd.17351
111. Reich K, Sullivan J, Arenberger P, et al. Secukinumab shows high and sustained efficacy in nail psoriasis: 2.5-year results from the randomized placebo-controlled TRANSFIGURE study. *Br J Dermatol*. 2021;184(3):425–436. doi:10.1111/bjd.19262
112. Nash P, Mease PJ, Kirkham B, et al. Secukinumab provides sustained improvement in nail psoriasis, signs and symptoms of psoriatic arthritis and low rate of radiographic progression in patients with concomitant nail involvement: 2-year results from the Phase III FUTURE 5 study. *Clin Exp Rheumatol*. 2022;40(5):952–959. doi:10.55563/clinexprheumatol/3nuz51
113. He F, Long FY, Zhang ZQ, Xia RY, Lu Y, Yin ZQ. Intramatrix injection of anti-interleukin-17A antibody for six patients with nail psoriasis. *Clin Exp Dermatol*. 2022;47(2):432–433. doi:10.1111/ced.14933
114. Gregoriou S, Tsiogka A, Tsimpidakis A, Nicolaidou E, Kontochristopoulos G, Rigopoulos D. Treatment of nail psoriasis with brodalumab: an open-label unblinded study. *J Eur Acad Dermatol Venereol*. 2021;35:e299–301. doi:10.1111/jdv.17055
115. Merola JF, Landewé R, McInnes IB, et al. Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor- α inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE). *Lancet*. 2023;401(10370):38–48. doi:10.1016/S0140-6736(22)02303-0
116. Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *J Dermatol*. 2018;45:1053–1062. doi:10.1111/1346-8138.14504
117. Gerdes S, Asadullah K, Hoffmann M, et al. Real-world evidence from the non-interventional, prospective, German multicentre PERSIST study of patients with psoriasis after 1 year of treatment with guselkumab. *J Eur Acad Dermatol Venereol*. 2022;36(9):1568. doi:10.1111/jdv.18218
118. Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPSAKE 1 trial. *Ann Rheum Dis*. 2022;81(2):225–231. doi:10.1136/annrheumdis-2021-221019
119. Megna M, Potestio L, Ruggiero A, Camela E, Fabbrocini G. Risankizumab treatment in psoriasis patients who failed anti-IL17: a 52-week real-life study. *Dermatol Ther*. 2022;35(7):e15524. doi:10.1111/dth.15524
120. Ismail FF, May J, Moi J, Sinclair R. Clinical improvement in psoriatic nail disease and psoriatic arthritis with tildrakizumab treatment. *Dermatol Ther*. 2020;33(2):e13216. doi:10.1111/dth.13216
121. Galluzzo M, Talamonti M, Cioni A, et al. Efficacy of tildrakizumab for the treatment of difficult-to-treat areas: scalp, nail, palmoplantar and genital psoriasis. *J Clin Med*. 2022;11(9):2631. doi:10.3390/jcm11092631
122. Brunasso A. Nail psoriasis improvement during tildrakizumab therapy: a real-life experience. *J Drugs Dermatol*. 2022;21(8):914–916. doi:10.36849/JDD.6828
123. Tham SN, Lim JJ, Tay SH, et al. Clinical observations on nail changes in psoriasis. *Ann Acad Med Singapore*. 1988;17:482–485.
124. Puri N, Mahajan BB. Nail changes in psoriasis – a profile. *J Pak Assoc Dermatol*. 2011;21:165–169.
125. Rigopoulos D, Baran R, Chiheb S, et al. Recommendations for the definition, evaluation, and treatment of nail psoriasis in adult patients with no or mild skin psoriasis: a dermatologist and nail expert group consensus. *J Am Acad Dermatol*. 2019;81(1):228–240. doi:10.1016/j.jaad.2019.01.072
126. Tosti A, Piraccini BM, Cameli N, et al. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol*. 1998;139(4):655–659. doi:10.1046/j.1365-2133.1998.02462.x
127. de Jong EM, Menke HE, van Praag MC, van de Kerkhof PC. Dystrophic psoriatic fingernails treated with 1% 5-fluorouracil in a nail penetration-enhancing vehicle: a double-blind study. *Dermatology*. 1999;199(4):313–318. doi:10.1159/000018281
128. Yamamoto T, Katayama I, Nishioka K. Topical anthralin therapy for refractory nail psoriasis. *J Dermatol*. 1998;25(4):231–233. doi:10.1111/j.1346-8138.1998.tb02386.x
129. Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis*. 2001;68(5):355–358.
130. Cannavo SP, Guarneri F, Vaccaro M, Borgia F, Guarneri B. Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo-controlled study. *Dermatology*. 2003;206(2):153–156. doi:10.1159/000068469
131. Rigopoulos D, Gregoriou S, Daniel Iii CR, et al. Treatment of nail psoriasis with a two-compound formulation of calcipotriol plus betamethasone dipropionate ointment. *Dermatology*. 2009;218(4):338–341. doi:10.1159/000202179
132. Balbás GM, Regaña MS, Millet PU. Tacalcitol ointment for the treatment of nail psoriasis. *J Dermatolog Treat*. 2009;20(5):308–310. doi:10.1080/09546630902787585
133. Saleem K, Azim W. Treatment of nail psoriasis with a modified regimen of steroid injections. *J Coll Physicians Surg Pak*. 2008;18(2):78–81.
134. Choudhary P, Mehta RD, Ghiya BC, Sharma D. Treatment of nail psoriasis with intramatrix methotrexate: an uncontrolled prospective study of 20 patients. *J Am Acad Dermatol*. 2021;84(2):526–528. doi:10.1016/j.jaad.2020.04.159
135. Mittal J, Mahajan B. Intramatrix injections for nail psoriasis: an open-label comparative study of triamcinolone, methotrexate, and cyclosporine. *Indian J Dermatol Venereol Leprol*. 2018;84(4):419. doi:10.4103/ijdv.IJDVL_73_16

136. Grover C, Daulatabad D, Singal A. Role of nail bed methotrexate injections in isolated nail psoriasis: conventional drug via an unconventional route. *Clin Exp Dermatol*. 2017;42(4):420–423. doi:10.1111/ced.13087
137. Clark A, Jellinek NJ. Intralesional injection for inflammatory nail diseases. *Dermatol Surg*. 2016;42(2):257–260. doi:10.1097/DSS.0000000000000621
138. SILIQ. Brodalumab (SILIQ) Prescribing information; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf. Accessed July 10, 2023.
139. Elewski B, Rich P, Lain E, Soung J, Lewitt GM, Jacobson A. Efficacy of brodalumab in the treatment of scalp and nail psoriasis: results from three phase 3 trials. *J Dermatol Treat*. 2020;2022:1–5.
140. Pinter A, Bonnekoh B, Hadshiew IM, Zimmer S. Brodalumab for the treatment of moderate-to-severe psoriasis: case series and literature review. *Clin Cosmet Investig Dermatol*. 2019;12:509–517. doi:10.2147/CCID.S211938
141. Ruggiero A, Potestio L, Martora F, Villani A, Comune R, Megna M. Bimekizumab treatment in patients with moderate to severe plaque psoriasis: a drug safety evaluation [published online ahead of print, 2023 Jun 19]. *Expert Opin Drug Saf*. 2023;1–8. doi:10.1080/14740338.2023.2218086
142. TREMFYA. Guselkumab (TREMFYA) Prescribing information; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761061s007lbl.pdf. Accessed July 10, 2023.
143. Foley P, Gordon K, Griffiths CEM, et al. Efficacy of guselkumab compared with Adalimumab and placebo for psoriasis in specific body regions. *JAMA Dermatol*. 2018;154(6):676–683. doi:10.1001/jamadermatol.2018.0793
144. Camela E, Potestio L, Fabbrocini G, Ruggiero A, Megna M. New frontiers in personalized medicine in psoriasis. *Expert Opin Biol Ther*. 2022;22(12):1431–1433. doi:10.1080/14712598.2022.2113872
145. Megna M, Tommasino N, Potestio L, et al. Real-world practice indirect comparison between guselkumab, risankizumab, and tildrakizumab: results from an Italian 28-week retrospective study. *J Dermatolog Treat*. 2022;33(6):2813–2820. doi:10.1080/09546634.2022.2081655
146. Machado Á, Torres T. Spotlight on risankizumab and its potential in the treatment of plaque psoriasis: evidence to date. *Psoriasis Targets Ther*. 2018;8:83–92. doi:10.2147/PTT.S165943
147. AbbVie. Skyrizi® (risankizumab-rzaa) injection, for subcutaneous use: US prescribing information; 2019. Available from: <http://www.rxabbvie.com>. Accessed April 20, 2022.
148. Ruggiero A, Picone V, Martora F, Fabbrocini G, Megna M. Guselkumab, risankizumab, and tildrakizumab in the management of psoriasis: a review of the real-world evidence. *Clin Cosmet Investig Dermatol*. 2022;15:1649–1658. doi:10.2147/CCID.S364640
149. Kristensen LE, Soliman AM, Papp K, et al. Effects of risankizumab on nail psoriasis in patients with active psoriatic arthritis: results from KEEPSAKE 1. *J Eur Acad Dermatol Venereol*. 2022;36(5):e389–e392. doi:10.1111/jdv.17931
150. AlAjlan A, Qasim R, Altassan F, Qadoumi T, AlKaff T. A case of nail psoriasis improved with treatment by risankizumab. *Oxf Med Case Rep*. 2022;2022(11):omac127. doi:10.1093/omcr/omac127
151. ILUMYA. Tildrakizumab (ILUMYA) Prescribing information; 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761067s000lbl.pdf. Accessed July 10, 2023.
152. Megna M, Potestio L, Fabbrocini G, Cinelli E. Tildrakizumab: a new therapeutic option for erythrodermic psoriasis? *Dermatol Ther*. 2021;34(5):e15030. doi:10.1111/dth.15030
153. Ruggiero A, Potestio L, Cacciapuoti S, et al. Tildrakizumab for the treatment of moderate to severe psoriasis: results from a single center preliminary real-life study. *Dermatol Ther*. 2022;35(12):e15941. doi:10.1111/dth.15941
154. Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) Br. *J Dermatol*. 2020;182:605–617.
155. Simpson K, Low ZM, Howard A, Kern JS. Successful management of treatment resistant nail psoriasis with tildrakizumab. *Australas J Dermatol*. 2021;62(3):390–393.
156. Canal-García E, Bosch-Amate X, Belinchón I, Puig L. Nail Psoriasis. Psoriasis ungueal. *Actas Dermosifiliogr*. 2022;113(5):481–490. doi:10.1016/j.ad.2022.01.006
157. Megna M, Potestio L, Fabbrocini G, Camela E. Treating psoriasis in the elderly: biologics and small molecules. *Expert Opin Biol Ther*. 2022;22(12):1503–1520. doi:10.1080/14712598.2022.2089020
158. Megna M, Camela E, Battista T, et al. Efficacy and safety of biologics and small molecules for psoriasis in pediatric and geriatric populations. Part I: focus on pediatric patients. *Expert Opin Drug Saf*. 2023;22(1):25–41. doi:10.1080/14740338.2023.2173170
159. Megna M, Camela E, Battista T, et al. Efficacy and safety of biologics and small molecules for psoriasis in pediatric and geriatric populations. Part II: focus on elderly patients. *Expert Opin Drug Saf*. 2023;22(1):43–58. doi:10.1080/14740338.2023.2173171
160. Ruggiero A, Martora F, Picone V, et al. The impact of COVID-19 infection on patients with psoriasis treated with biologics: an Italian experience. *Clin Exp Dermatol*. 2022;47(12):2280–2282. doi:10.1111/ced.15336
161. Megna M, Potestio L, Battista T, et al. Immune response to COVID-19 mRNA vaccination in patients with psoriasis undergoing treatment with biologics. *Clin Exp Dermatol*. 2022;47(12):2310–2312. doi:10.1111/ced.15395
162. Martora F, Villani A, Battista T, Fabbrocini G, Potestio L. COVID-19 vaccination and inflammatory skin diseases. *J Cosmet Dermatol*. 2023;22(1):32–33. doi:10.1111/jocd.15414
163. Martora F, Marasca C, Fabbrocini G, Ruggiero A. Strategies adopted in a southern Italian referral centre to reduce Adalimumab discontinuation: comment on ‘Can we increase the drug survival time of biologic therapies in hidradenitis suppurativa?’. *Clin Exp Dermatol*. 2022;47(10):1864–1865. doi:10.1111/ced.15291
164. Martora F, Fabbrocini G, Nappa P, Megna M. Reply to ‘Development of severe pemphigus vulgaris following SARS-CoV-2 vaccination with BNT162b2’ by Solimani et al. *J Eur Acad Dermatol Venereol*. 2022;36(10):e750–e751. doi:10.1111/jdv.18302
165. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol*. 2022;18(8):465–479. doi:10.1038/s41584-022-00798-0
166. Reich K, Conrad C, Kristensen LE, et al. Network meta-analysis comparing the efficacy of biologic treatments for achieving complete resolution of nail psoriasis. *J Dermatolog Treat*. 2022;33(3):1652–1660. doi:10.1080/09546634.2021.1892024

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