Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Nail Psoriasis: An Updated Review of Currently Available Systemic Treatments

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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

Received: 8 May 2023
Accepted: 8 July 2023
Published: 24 July 2023

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 injections[133] 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 at 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 NAPSI 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	NAPSI 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 NAPSI score worsened from 20 to 20.5. Three patients improved 50% of the initial NAPSI 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 NAPSI 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 NAPSI score reduced by 75% at 24 weeks

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https://doi.org/10.2147/CCID.S417679

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

https://doi.org/10.2147/CCID.S417679

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 NAPSI 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, NAPSI 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 NAPSI 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 mNAPSI.
Infliximab	Fabroni et al, 2011[55]	Real-life retrospective study	48	5 mg/kg	38 weeks	The mean NAPSI ± 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 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; $p < 0.0001$).

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 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]
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	NAPSI 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 NAPSI75 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 NAPSI90 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	mNAPSI 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	NAPSI improved from 50.34 (baseline) to 20.5 (W24) with a further reduction to 10 (W52).

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https://doi.org/10.2147/CCID.S417679

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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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https://doi.org/10.2147/CCID.S417679

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 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
Bimekizumab	Merola et al, 2023[115]	Phase III trial	556	Label dosage	16 weeks	Among patients with mNAPSI greater than 0 at baseline, at week16 mNAPSI 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 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; improvement was maintained to week 52
Guselkumab	Gerdes et al, 2022[117]	Real-life prospective study	297	Label dosage	52 weeks	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
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 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.

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https://doi.org/10.2147/CCID.S417679

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. NAPSI and mNAPSI scores before therapy, every 2 months during therapy, and 6 months after treatment were evaluated. The mean percentage of reduction of the NAPSI score after treatment was 41%; the mean percentage of reduction of the mNAPSI score of the target nail was 50%. Complete or almost complete clearing of nail lesions was achieved in 25% of patients. Ricceri et al[17] 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 NAPSI 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 mNAPSI (score = 9).[19]

However, an additional study in the literature reported a worsening of NAPSI 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. NAPSI was collected in the first evaluation, after 2 and 4 months. Nails of both hands were evaluated. Mean NAPSI at baseline was 20 and the final score 20.5. Seven patients worsened in the final score. Three patients improved 50% of the initial NAPSI 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 NAPSI 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 NAPSI, 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 NAPSI 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 NAPSI at the end of week 16 compared with control group, although PASI decreased significantly. Rate of NAPSI 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 subcutaneousMTX, 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 NAPSI-50 score (50% reduction from baseline in NAPSI 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 NAPSI 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 NAPSI 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 NAPSI 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-naive 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, NAPSI mean change from baseline was −48.1% to −51.1AEs in ≥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. mNAPSI75 response, 75% or greater reduction over baseline mNAPSI, 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 al[44] evaluated efficacy, US parameters and safety of apremilast for NP conducting a prospective cohort study including adult patients with plaque and NP with a NAPSI 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 NAPSI improved by 53%. US parameters improved from week 16 onwards. Target nail NAPSI 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 NAPSI 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 NAPSI of 4 (improvement of 90%). The other patient was affected by plaque psoriasis and nail involvement with a NAPSI 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 NAPSI over 24 weeks. At week 24, mean NAPSI had decreased in both etanercept groups [BIW/QW group: -4.3 ($p < 0.0001$); QW/QW group: -4.4 ($p < 0.0001$)]. Mease et al[26] examined the efficacy of MTX monotherapy relative to that of etanercept monotherapy and their combination in 588 patients. There was no significant difference in mNAPSI changes between the two monotherapies at week 24, while combining therapy showed a greater decrease in mNAPSI 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. NAPSI 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 NAPSI 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 al[48] 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 fingernails[50]. 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. NAPSI 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. NAPSI 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 ± SD was 49.68 ± 25.99. The mean NAPSI ± 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 ± 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. administrated 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 ± 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-a 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-alpha (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 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. 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 >100kg) at baseline and week 4 and every 12 weeks thereafter.[87] NAPSI score was assessed at baseline at weeks 16, 28, and 40. 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. Moreover, NAPSI 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 NAPSI score of 4.0 ± 2.0. At week 12, the mean percent improvement in NAPSI 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 ± 27.8%). 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. A post hoc analysis of a phase IV, multicenter, open-label, real-world observational clinical trial, the MARCOPOLO study, was conducted to establish standard NAPSI improvement rates in patients treated with ustekinumab.[89] Ustekinumab was administered over a period of 52 weeks. NAPSI scores were recorded at baseline, 28 weeks, and 52 weeks. NAPSI 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% NAPSI 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 NAPSI 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 NAPSI 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 NAPSI, only pitting showed statistically significant improvement. Similarly, oil-drop discoloration was the only characteristic of the bed component of NAPSI 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 NAPSI score for the 13 patients was 22.3 and mNAPSI at week 0 was 6.3. The mean NAPSI score at the end of week 12 was 14.8 (range, 0–58) and the mean mNAPSI score for the target nail was 5.2 (range, 0–10).

The mean percentages of reduction of the NAPSI score and mNAPSI score were 31.8% and 13.3%, respectively. At the end of week 12, for two of our 13 patients (15%), NAPSI 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 NAPSI 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 NAPSI 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 NAPSI 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 NAPSI = 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 NAPSI 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 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, $p < 0.001$). 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 4weeks (Q4W) or every 2 weeks (Q2W) after receiving a 160 mg starting dose. Ixekizumab demonstrated significant improvement in NAPSI score at week 2 vs etanercept (5.1 vs −7.9%, p = 0.024). At week 12, greater mean percentage NAPSI 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 NAPSI 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 NAPSI 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 (NAPSI > 1) or significant NP (fingernail NAPSI ≥16 and ≥4 fingernails involved) at baseline.[105] Efficacy outcomes reported through week 264 included the mean percentage improvements from baseline in NAPSI score and the proportion of patients achieving NP resolution (NAPSI = 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 NAPSI was 69.87 ± 32.51, median 66. After 6 weeks of treatment with secukinumab 300 mg mean NAPSI 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, NAPSI 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 NAPSI 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 mNAPSI. At baseline, 66.6% patients (663/996) had concomitant NP. Secukinumab reduced mNAPSI 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 administrated by intramatricial 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 intramatricial 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 NAPSI 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 NAPSI was 73.2% and 18.3%, respectively ($p < 0.01$) between the treated nails and the control. The mean improvement rate of NAPSI 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 NAPSI 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 intramatricial 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 NAPSI of ≥6. Nail clearance efficacy was measured by improvement in mean NAPSI (range 0–32), percentage of responders with a NAPSI of 0, and percent improvement rates from baseline NAPSI.

Endpoints included mean NAPSI improvement and achievement of a NAPSI 0 score (absence of all parameters in the NAPSI). Comparison of brodalumab and ustekinumab demonstrated an improved mean NAPSI 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 NAPSI 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 NAPSI 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 NAPSI 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 TNFα 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 week16 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 ≥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.

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