Efficacy of Biologics Targeting Tumour Necrosis Factor-alpha, Interleukin-17 -12/23, -23 and Small Molecules Targeting JAK and PDE4 in the Treatment of Nail Psoriasis: A Network Meta-analysis

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The comparative efficacy of registered anti-psoriatic biologics and small molecules in treating nail symptoms has not been systematically evaluated. The aim of this study was to perform a network meta-analysis to determine the efficacy of biologics and small molecules in nail psoriasis. A Bayesian network meta-analysis of 17 randomized clinical trials (a total of 6,053 nail psoriatic patients) was performed, comparing the short-term (week 10–16) efficacy of biologics and small molecules in the treatment of nail psoriasis. All active treatments were found to be superior to placebo. Ixekizumab 80 mg every 4 weeks (Nail Psoriasis Severity Index (NAPSI) % improvement, Surface Under the Cumulative Ranking (SUCRA)=0.92) and etanercept 50 mg twice weekly (probability of achieving NAPSI 50, SUCRA=0.82) proved the best short-term treatment options. However, efficacy end-points in psoriasis trials were not optimized for nail assessment, and outcome parameters were highly heterogeneous, limiting comparability. In conclusion, outcome parameters and efficacy endpoints of nail psoriasis trials should be standardized.

Key words: nail psoriasis; efficacy; biologics; network meta-analysis; Nail Psoriasis Severity Index.

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SIGNIFICANCE

Psoriasis, a chronic inflammatory skin disease, often affects the nails. Nail psoriasis is an embarrassing condition that presents a therapeutic challenge. New treatments, such as the so-called biological therapies, are highly effective in treating psoriatic skin symptoms. Although many of these treatments have proved useful in treating nail symptoms, to date, their efficacy for treating nail psoriasis has not been determined. This study systematically analysed and compared the short-term efficacy of the new medications used for treating nail psoriasis, and determined their therapeutic ranking based on the probability of the treatment improving psoriatic nail symptoms.

Nail psoriasis is an embarrassing condition with a high unmet medical need (1). Its negative impact regarding health-related quality of life and impaired ability to perform daily activities are known (2). Prevalence of nail psoriasis is as high as 50% among psoriatic patients, and patients are often stigmatized (3). In addition, nail psoriasis can be an indicator for psoriatic arthritis (PsA) (4). Although a variety of therapies is available for both skin and nail psoriasis, treatment of nail psoriasis remains a challenge (5). Recent recommendations, based on a dermatologist and nail expert group consensus (6), specify which treatments should be used as first-line in nail psoriasis. Usually medications used for treating skin psoriasis or PsA are also recommended for treating nail psoriasis. The comparative efficacy of these medications for treating both skin and joint symptoms has been analysed in several network meta-analyses (NMAs) (7–10). Although several randomized controlled trials (RCTs) have confirmed that biologics (TNF inhibitors, interleukin inhibitors) and novel small molecules (PDE4 inhibitors, JAK inhibitors) are effective in treating not only skin and joint, but nail also psoriasis symptoms, the comparative efficacy of registered anti-psoriatic biologics in treating nail symptoms has not been evaluated systematically. Similar to RCTs, NMAs are the mainstays of evidence-based medicine, because they allow comparison of the effects of multiple interventions with each other by using advanced statistical techniques. In addition, indirect comparison of interventions is possible through a common comparator, as well as ranking by efficacy, thereby guiding guideline developers and clinicians. This study performed an NMA of RCTs of biological therapies in skin psoriasis and/or PsA with a secondary endpoint of nail psoriasis, to determine the efficacy of these therapies to treat nail psoriasis.

MATERIALS AND METHODS

Study protocol

The NMA was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (code CRD420191143317; http://dx.doi.org/10.17632/mw2b9fcrhr.1). The systematic review (SR) is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (11).

Search and eligibility

MEDLINE (via PubMed), CENTRAL and Embase were searched up to April 2019 for RCTs with the following search key: "nail" OR "psoriasis" AND random*. No filter was used. The included RCTs compared the efficacy of TNFα, IL-17, IL12/23, IL-23 and JAK and PDE4 inhibitors with placebo or active comparator in psoriatic patients with nail involvement. Interventions included biologics (ixekizumab (12, 13), etanercept (14), infliximab (15), ustekinumab (16, 17), tofacitinib (18–20), apremilast (21–25), secukinumab (26), adalimumab (27), guselkumab (28–30), golimumab (31), and risankizumab (32)). The severity of nail psoriasis was assessed by the objective scale of the Nail Psoriasis Severity Index (NAPSI) (33). Trial objectives were to assess target fingernail (usually the most severe nail, NAPSI 1–8) or overall fingernail (all fingernail, NAPSI 1–80).

Selection, data collection and risk of bias assessment

Trials were selected and assessed independently by 2 investigators (SJ, SZ) in 3 phases by title, abstract and full-texts. Interventions were evaluated based on NAPSI percentage improvement compared with baseline, with measure of dispersion at week 10–16, and the number of patients achieving at least 50%, 75% or 100% reduction in NAPSI, with measure of dispersion at week 10–16. Missing values were requested from the authors of the papers via e-mail. RCTs were assessed with the Cochrane Risk of Bias Tool (34).

Statistical analysis

A Bayesian model was used to perform pairwise meta-analyses and NMA with the random effect model. The network model was performed under consistency assumption based on deviance information criterion (DIC, a measure to test model fit) since that proved to be equivalent to the consistency model (DIC: 63.91) and the inconsistency model (DIC: 64.09). It was not possible to use node-splitting analysis (the comparison of direct and indirect evidence from a loop) to test consistency assumption, because there was insufficient amount of information from the comparisons in the network. Risk ratios (RR) and, for NAPSI 50 and mean difference (MD) for NAPSI percentage improvement (continuous) with 95% credible intervals (CrI), were used. The model was optimized and posterior samples were generated using the Monte-Carlo methods running in 4 chains. At least 20,000 adaptation iterations were set to obtain convergence and 10,000 stimulation iterations. Network estimates (pooled direct and indirect data) of each intervention compared with placebo and with other interventions are presented in forest plots, summarized in a league table (as shown in the Results section). Interventions were also ranked by Surface Under the Cumulative Ranking (SUCRA), a numerical presentation of the overall ranking, which presents a single number (between 0 and 1) associated with each treatment. The higher the SUCRA value, the more likely the intervention is within the top interventions. Following Puhan's recommendations (35), funnel plots were created for both outcomes and Egger's tests were performed to assess small-study effect. All calculations were performed with R (V. 3.5.2) package gemtc (V. 0.8–2) along with the Markov Chain Monte Carlo engine JAGS (V. 3.4.0) and STATA 17.0 (StataCorp LLC, Texas, USA).

RESULTS

Study selection and characteristics of the included studies

The flowchart of the selection process is shown in **Fig. 1**. Altogether 34 studies were included in the SR, 17 of which (with a total of 6,053 patients) fit the network

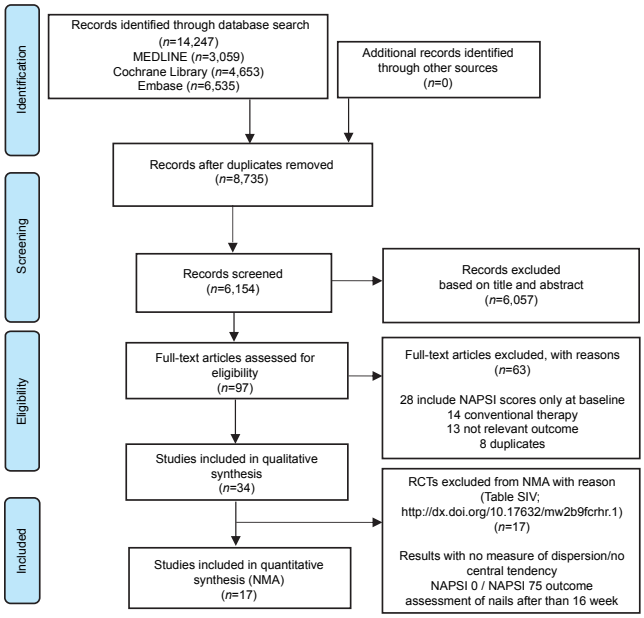

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

(**Table I**). At baseline, the mean age of patients ranged from 41 to 54 years, males 34.4–100%, patients with PsA 0–100%, target fingernail NAPSI 3.3–6.0 and overall NAPSI ranged from 18.7–47.9. Fifteen interventions, including placebo treatment, enrolled in the network regarding NAPSI percentage improvement at week 10–16 and 9 interventions (including placebo treatment) were analysed regarding NAPSI 50 at week 12–16 (**Fig. 2**). The majority of the studies assessed the primary endpoints at week 10, 12 or 16.

Relative efficacy

Regarding NAPSI percentage improvement (week 10–16), **Table II** summarizes the results in a league table. Ixekizumab 80 mg every 4 weeks and ixekizumab 80 mg every 2 weeks were more effective than infliximab 5 mg/kg, ustekinumab 90 mg, ustekinumab 45 mg, adalimumab 40 mg, guselkumab 50 mg, guselkumab 100 mg and apremilast 30 mg. Placebo was significantly worse than all the biologics included in the analysis.

Ranking of treatment options by efficacy

Regarding NAPSI percentage improvement (week 10–16) given in SUCRA, ixekizumab 80 mg every 4 weeks had the highest probability of being the best treatment (0.92), followed by ixekizumab 80 mg every 2 weeks (0.90) and ixekizumab 75 mg (0.78). The other interventions yielded lower SUCRAs (0.11–0.74); not surprisingly, placebo proved to be the worst option, with a SUCRA of 0.00.

Regarding NAPSI 50 (week 12–16) given in SUCRA, etanercept 50 mg twice and once weekly had the highest efficacy indicated by the ranking table probability (0.82

Table I. Characteristics of the studies included in the network meta-analysis (NMA)

Author (ref; year)	Setting: country; recruitment period; centre	All patients (nail psoriatic patients, % of total)	Age Mean±SD	Sex (male %)	PsA patients (%)	Nail psoriatic patients *n*	Interventions – therapeutic regimen	NAPSI assessment (timing in weeks)
Blauvelt et al. (28; 2017)	USA; 2014–2016; multicentre	837 (58)	43.9±12.7	72.9	19.5	194	Guselkumab 100 mg Q8W[1] sc.	Target nail (16)
			42.9±12.6	74.6	18.6	191	Adalimumab 40 mg[2] sc.	
			44.9±12.9	68.4	17.2	99	Placebo	
Foley et al. (29; 2018)	Melbourne; 2014–2016; multicentre	1,829 (51)	43.8±12.4	71.4	18.5	420	Guselkumab 100 mg Q8W[1] sc.	Target nail (16)
			43.0±12.4	72.0	18.2	297	Adalimumab 40 mg[2] sc.	
			43.9±12.6	69.2	18.0	211	Placebo	
Gooderham, et al. (15; 2016)	Canada; NR; NR	250 (59)	NR	NR	NR	52	Apremilast 30 mg BID[3] p.o	Target nail (16)
						50	Etanercept 50 mg QW[4] sc.	
						46	Placebo	
Igarashi et al. (16; 2012)	Japan; 2008–2010; Japan (35 sites)	158 (65)	45	82.8	9.4	44	Ustekinumab 45 mg[5] sc.	Target nail (12)
			44	75.8	11.3	40	Ustekinumab 90 mg[5] sc.	
			49	83.9	3.1	18	Placebo	
Jackson, et al. (24; 2018)	USA; NR; NR	221 (38)	NR	NR	NR	83	Apremilast 30 mg BID[3] p.o	Target nail (NAPSI≥1) (16)
							Placebo	
Leonardi, et al. (12; 2012)	USA; 2010–2011; multicentre	60 (100)	48.0±11	57.0	NR	13	Ixekizumab 10 mg sc.	Overall fingernail (NAPSI>0) (12)
			46.0±15	60.0		10	Ixekizumab 25 mg sc.	
			46.0±13	66.0		10	Ixekizumab 75 mg[6] sc.	
			46.0±13	50.0		10	Ixekizumab 150 mg[6] sc.	
			45.0±13	52.0		17	Placebo	
Merola, et al. (18; 2017)	USA; 1 year; multicentre	1,196 (100)	46	78.2	24.8	487	Tofacitinib 5 mg BID[3] p.o	Overall nail (16)
			45	77.1	23.5	476	Tofacitinib 10 mg BID[3] p.o	
			45	75.1	21.0	233	Placebo	
Ohtsuki, et al. (30; 2018)	Japan; 2015–2016; Japan (35 sites)	192 (66)	47.8±11.1	74.6	15.9	40	Guselkumab 100 mg Q8W[1] sc.	Target nail (16)
			50.1±12.7	67.7	16.9	44	Guselkumab 50 mg Q8W[1] sc.	
			48.3±10.6	84.4	15.6	42	Placebo	
Ortonne, et al. (14; 2013)	France; 2007–2009; multicentre	72 (100)	46.3±13.5	72.2	NR	36	Etanercept 50 mg BIW[7] sc.	Overall nail (12)
			45.4±9.2	72.7		33	Etanercept 50 mg QW[4] sc.	
Papp, et al. (21; 2012)	Canada; NR; NR	352 (63)	44	63.0	NR	57	Apremilast 30 mg BID[3] p.o	NR (16)
						55	Apremilast 20 mg BID[3] p.o	
						55	Apremilast 10 mg BID[3] p.o	
						54	Placebo	
Papp, et al. (22; 2015)	Canada; 2010–2012; multicentre (72 sites)	844 (66)	45.8±13.1	67.4	24.2	363	Apremilast 30 mg BID[3] p.o	Target nail (NAPSI≥1) (16)
			46.5±12.7	68.8	19.5	195	Placebo	
Paul, et al. (23; 2015)	France; 2010–2012; multicentre (40 sites)	411 (65)	45.3±13.1	64.2	15.4	175	Apremilast 30 mg BID[3] p.o	Target nail (NAPSI≥1) (16)
			45.7±13.4	73.0	7.7	91	Placebo	
Poulin, et al. (27; 2013)	Canada; NR; NR	72 (50)	49.0±11.4	42.9	14.3	28	Adalimumab 40 mg[2] sc.	Target nail (NAPSI 0–8) (16)
			54.0±11.4	34.8	4.3	8	Placebo	
Reich, et al. (15; 2005)	Germany; NR; NR	378 (81)	42.6±11.7	69.0	31.0	240	Infliximab 5 mg/kg[8] iv.	Target nail (10)
			43.8±12.6	79.0	29.0	65	Placebo	
Rich, et al. (17; 2014)	USA; 5 year; multicentre	766 (71)	45.9±12.3	75.8	31.3	182	Ustekinumab 45 mg[9] sc.	Target nail (12)
			46.0±10.9	77.0	38.0	187	Ustekinumab 90 mg[9] sc.	
			45.1±11.1	77.8	36.9	176	Placebo	
Van de Kerkhof, et al. (13; 2017)	The Netherlands; 1.5 year; multicentre	1,346 (60)	45.5±12.5	71.0	22.3	229	Ixekizumab 80 mg Q2W[10] sc.	Total fingernail (NAPSI>0) (12)
			45.9±11.6	78.0	23.2	228	Ixekizumab 80 mg Q4W[11] sc.	
			46.3±13.5	78.0	22.5	236	Etanercept 50 mg BIW[7] sc.	
			47.5±11.3	79.0	22.4	116	Placebo	
Zhang, et al. (20; 2017)	China; 2013–2015; asian	266 (44)	40.7±11.3	73.9	6.8	38	Tofacitinib 5 mg BID[3] p.o	NR (16)
			41.0±12.0	74.4	4.4	40	Tofacitinib 10 mg BID[3] p.o	
			41.7±13.7	70.5	9.1	38	Placebo	

Demography and characteristic of the included 17 studies for NMA.
[1]0, 4 then every 8 weeks, [2]every 2 weeks, after 80 mg at week 0, and 40 mg at week 1, [3]twice daily, [4]once weekly, [5]at weeks 0, 4, 12, [6]at weeks 0, 2, 4, 8, 12, 16, [7]twice weekly, [8]at weeks 0, 2, 6 then every 8 weeks, [9]at weeks 0, 4, 16, [10]every 2 weeks, after a 160 mg starting dose, [11]every 4 weeks, after a 160 mg starting dose.
SD: standard deviation; NR: not reported; PsA: psoriatic arthritis; NAPSI: Nail Psoriatic Severity Index.

and 0.77, respectively), followed by adalimumab 40 mg every 2 weeks (0.74). The other interventions yielded lower SUCRAs (0.21–0.68); not surprisingly placebo had the lowest probability of being the best option for treating nail psoriasis with a SUCRA of 0.05; Supplementary data available online).

Systematic review

Altogether, 34 studies were eligible for the SR. Five RCTs investigating the efficacy of ixekizumab 80 mg every 4 and 2 weeks (36–42) among psoriatic patients with nail involvement were included in the SR. Two RCTs were found with ustekinumab 45/90 mg, 2 trials with adalimumab 40 mg every 2 weeks, (43) and another 2 trials with apremilast 30 mg twice daily (44). In addition, the SR included 1 RCT in both groups with the following biologics: tofacitinib 5 and 10 mg twice daily, (45) etanercept 50 mg twice weekly, guselkumab 100 mg every 8 weeks, (46) golimumab 50 and 100 mg every 4 weeks, (31) infliximab 5 mg/kg, (47) risankizumab 90 and 180 mg (32) and secukinumab 150 and 300 mg (26) (see Supplementary data available online).

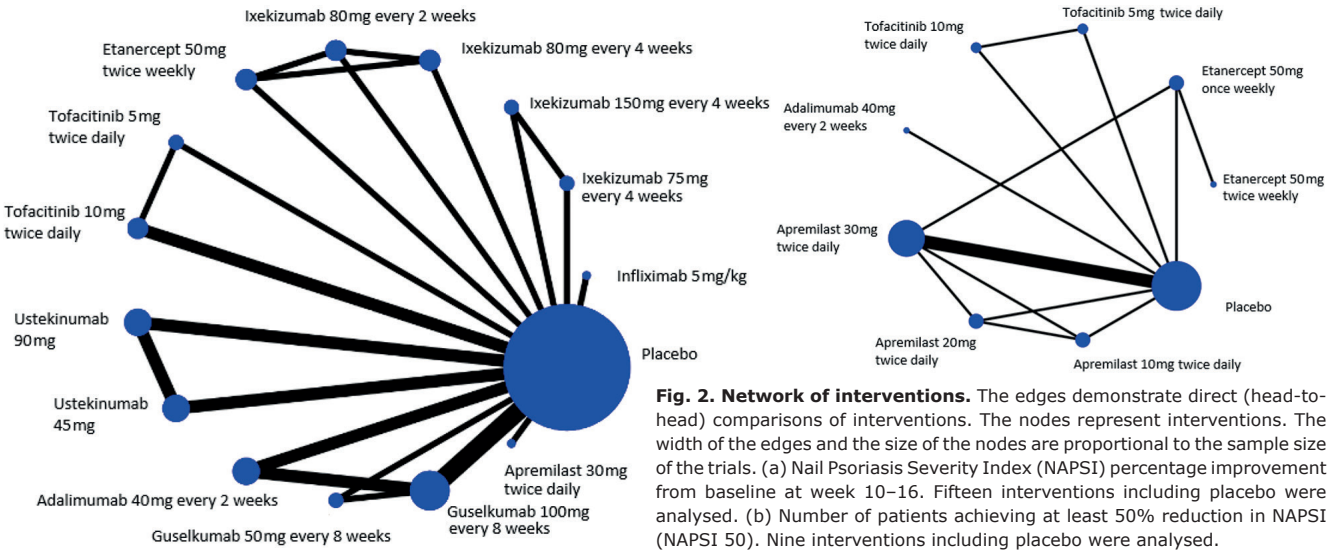

Fig. 2. Network of interventions. The edges demonstrate direct (head-to-head) comparisons of interventions. The nodes represent interventions. The width of the edges and the size of the nodes are proportional to the sample size of the trials. (a) Nail Psoriasis Severity Index (NAPSI) percentage improvement from baseline at week 10–16. Fifteen interventions including placebo were analysed. (b) Number of patients achieving at least 50% reduction in NAPSI (NAPSI 50). Nine interventions including placebo were analysed.

For risk of bias within the individual studies and strength of the NMA (Supplementary data).

DISCUSSION

Summary of findings

Despite considerable progress in the treatment of psoriatic skin symptoms, nail psoriasis has remained a therapeutic challenge. Although several SRs and meta-analyses regarding the efficacy of biological therapies for patients with moderate-to-severe skin psoriasis exist, there is no NMA assessing the therapeutic efficacy of novel anti-psoriatic medications in nail psoriasis. A Cochrane SR was carried out by de Vries in 2013 (48) and SRs regarding treatment recommendations in nail psoriasis were also performed by Cassell (49) and Armstrong (50). However, many of the currently used anti-psoriatic therapies were not available at the time of these reviews, and the comparative efficacy of therapies was not analysed. The current SR and NMA set out to evaluate and compare registered biological therapies (TNF-inhibitors, IL-17 inhibitors, ustekinumab and IL-23 inhibitors) and novel anti-psoriatic small molecules (tofacitinib and apremilast) for their therapeutic efficacy in nail psoriasis. The current SR included 34 RCTs and 9,383 patients; however, only 17 RCTs (6,053 patients) could be evaluated in the NMA (the others had to be excluded mostly due to missing outcome values). The current study found that all active treatments were superior to placebo: both in the NAPSI percentage and NAPSI

Table II. Network meta-analysis of efficacy (Nail Psoriasis Severity Index (NAPSI) percentage improvement at week 10–16)

Infliximab 5 mg/kg														
27 (−7.5; 63)	Ixekizumab 75 mg													
24 (−10; 58)	−2.5 (−35;29)	Ixekizumab 150 mg												
38 (9.9; 66)	12 (−29; 50)	14 (−24; 53)	Ixekizumab 80 mg Q4W[1]											
37 (7.4; 64)	9.5 (−30; 49)	12 (−25; 51)	−1.7 (−21; 18)	Ixekizumab 80 mg Q2W[2]										
22 (−6.7; 49)	−4.7 (−47; 35)	−2.4 (−41; 36)	−17 (−36; 2.7)	−15 (−34; 4.8)	Etanercept 50 mg BIW[3]									
4.1 (−27; 37)	−22 (−62; 18)	−19 (−59; 20)	−35 (−67; 1.5)	−32 (−67; 2.9)	−18 (−52; 19)	Tofacitinib 5 mg								
21 (−7.4; 51)	−6.3 (−44; 32)	−3.3 (−40; 35)	−18 (−49; 17)	−16 (−48; 19)	−1.2 (−33; 34)	17 (0.72; 33)	Tofacitinib 10 mg							
−20 (−40; 2)	**−46 (−79; −14)**	**−43 (−75;−11)**	**−58 (−83; −33)**	**−56 (−81; −31)**	**−41 (−66; −16)**	−23 (−54; 5.8)	**−40 (−68; −15)**	Ustekinumab 90 mg						
−18 (−39; 4.2)	**−45 (−78; −12)**	**−42 (−75;−8.8)**	**−56 (−82; −30)**	**−55 (−81; −29)**	**−40 (−65; −14)**	−22 (−53; 7)	**−38 (−68; −13)**	1.4 (−12; 15)	Ustekinumab 45 mg					
8.2 (−12; 28)	−18 (−52; 13)	−16 (−48;15)	**−30 (55; −5.8)**	**−28 (−53; −3.2)**	−13 (−39; 12)	−4.3 (−27; 32)	−12 (−40; 13)	**27 (11; 43)**	**26 (9.2; 43)**	Adalimumab 40 mg				
−2.5 (−29;23)	−29 (−66; 6)	−26 (−62; 8.4)	**−41 (−70; −11)**	**−39 (−69; −9.2)**	−24 (−54; 7.4)	−6.7 (−40; 25)	−23 (−53; 6.7)	17 (−6.6; 39)	15 (−8.5; 39)	−11 (−31; 10)	Guselkumab 50 mg			
4.5 (−15; 24)	−22 (−55; 8.8)	−19 (−51;11)	**−34 (−58; −9.5)**	**−32 (−56; −7.1)**	−17 (−42; 8.2)	0.49 (−29; 29)	−16 (−43; 8.3)	**24 (8.2; 39)**	**23 (6.3; 38)**	−3.8 (−12; 5.2)	6.9 (−12; 26)	Guselkumab 100 mg		
−3.5 (−25; 19)	−30 (−64; 2.2)	−27 (−60; 6.3)	**−41 (−68; −16)**	**−40 (−66; −13)**	−25 (−52; 2.1)	−7.5 (−39; 22)	−24 (−53; 2.9)	16 (−2.2; 34)	15 (−4.1; 34)	−12 (−28; 5.9)	−0.79 (−24; 24)	−7.8 (−24; 9.1)	Apremilast 30 mg	
−32 (−49; −15)	**−59 (−90; −29)**	**−56 (−86; −26)**	**−70 (−92; −48)**	**−69 (−91; −46)**	**−54 (−76; −31)**	**−36 (−64; −11)**	**−53 (−78; −30)**	**−13 (−25; −0.57)**	**−14 (−27; −1.3)**	**−41 (−50; −30)**	**−30 (−49; −9.8)**	**−37 (−46; −28)**	**−29 (−43; −15)**	Placebo

Comparison of efficacy of all interventions included in the network meta-analysis (NAPSI percentage improvement, at week 10–16). Shaded cells: interventions with regimen. Unshaded cells: efficacy values (mean difference (95% confidence interval; 95% CI) between interventions. Statistically significant differences are in bold. [1]Every 4 weeks, [2]every 2 weeks, [3]twice weekly.

50 analysis. For NAPSI percentage improvement, the IL-17 inhibitor ixekizumab 80 mg every 4 weeks and every 2 weeks ranked first and second, respectively, followed by ixekizumab 75 mg. Interestingly, the IL-12/23 inhibitor ustekinumab ranked second and third to last. Surprisingly, the IL-23 inhibitor guselkumab also ranked worse than the TNF-inhibitor adalimumab, although in head-to-head comparison RCTs guselkumab was found to be superior to adalimumab in treating skin symptoms (both regarding IGA and PASI 90 at week 16) (29). When NAPSI 50 was used as the outcome measure, etanercept 50 mg twice and once weekly ranked first and second, respectively, and adalimumab 40 mg twice weekly scored third. It must be emphasized, however, that, in this analysis, only RCTs with etanercept, adalimumab, tofacitinib and apremilast could be included; there was no trial with IL-17, IL-12/23 or IL-23 inhibitors. In the current NMA ixekizumab was associated with the highest efficacy for nail psoriasis, while both the IL-23 guselkumab and the IL-12/23 ustekinumab ranked surprisingly low. In a recent meta-analysis, Sawyer et al (51) found that brodalumab, ixekizumab, guselkumab and risankizumab had the highest benefit for skin symptoms. This suggests that the efficacy of biologics may be different in treating skin and nail psoriasis. This is probably due to the different pathogenesis of skin and nail psoriasis symptoms, as well as to the different mode of action of biologics, as shown by the opposing skin and nail results in the guselkumab vs adalimumab trial (29). As nail (especially matrix) psoriasis is known to be associated with PsA, it is tempting to assume that systemic anti-psoriatic agents may perform similarly in nail and PsA studies. In a recent meta-analysis secukinumab was found superior in terms of ACR20 and ACR50 to ustekinumab, while for PASI 75 the ranking was opposite (52). In a more recent NMA, however, ustekinumab 90 mg had almost the same efficacy as ixekizumab (Q2: 80 mg every 2 weeks, after a 160 mg starting dose Q4: 80 mg every 4 weeks, after a 160 mg starting dose) for ACR20 response and PASI 75 response during induction therapy, while ustekinumab 45 mg was less efficacious both in treating skin and joint symptoms (53). According to the recommendation of the National Psoriasis Foundation, (54) ustekinumab, adalimumab, etanercept and infliximab should be regarded as the most appropriate therapeutic option for nail psoriasis. These results provide additional information when choosing the optimal treatment for psoriatic patients who are candidates for systemic therapy. In case clearance of nail symptoms is of considerable importance, according to the current results, the best option would be the IL-17 inhibitor ixekizumab, whereas ustekinumab or guselkumab are potentially less effective.

Study limitations

Several points must be taken into consideration when analysing these results. First, extensive heterogeneity of outcome measure reporting was found concerning nail psoriasis in the RCTs reviewed. At least 7 different nail scoring systems were used, making the comparison of the results rather difficult. We chose the 2 most commonly used assessment tools: (*i*) proportional improvement of the NAPSI score (NAPSI percentage) and (*ii*) the likelihood of achieving 50% reduction in the NAPSI score (NAPSI 50). RCTs, using different nail assessment methods (such as modified NAPSI, Psoriasis Nail Severity Score, Nail Area Severity), had to be excluded from the NMA in order to meet the transitivity condition. This led to considerable reduction in the number of RCTs in the NMA, and resulted in the exclusion of some therapies from the analysis. For example, a recent trial investigating the efficacy of secukinumab (55), with a total of 304 psoriatic patients, had to be excluded from the current analysis, since nail severity and improvement was assessed by a composite fingernail score. In addition, several RCTs had to be excluded from the analysis due to missing outcome values; measure of dispersion or central tendency (for a complete list of reasons for exclusion from the network meta-analysis see the Supplementary data available online). For example this was the reason why another RCT with secukinumab, although it showed excellent efficacy for nail psoriasis (26), could not be included in the current analysis. In an attempt to elaborate on the results of the 16 RCTs not included in the network analysis, missing values were requested from the corresponding authors of the original trials; however, none of them responded.

Secondly, in the current NMA we could only include short-term observations regarding the efficacy of biologics in nail psoriasis. This may limit the relevance of the study, as nail psoriasis improvement is considerably slower than that of the skin. Most analysed RCTs were designed to assess the efficacy of the medications on skin symptoms, for which almost complete response can be expected within 10–16 weeks. Thus, in most RCTs, this time period was chosen as the assessment time. In case of nail symptoms, it may take significantly longer (26–52 weeks) to reach optimal results, and between week 10 and 16 nail psoriasis severity values may change dynamically. This could lead to potential bias in favour of drugs with fast onset of action (e.g. TNF- and IL-17 inhibitors), and trials with later (week 16) assessment time-points. Based on the methodology of NMA, a common comparator arm is needed for the evaluation of the efficacy of the therapeutic agents. As most psoriasis trials are placebo-controlled cross-over studies, the comparator arm is terminated after the primary endpoint (usually at week 10–16). Therefore, unless the trial was designed to assess week 24–52 efficacy as the primary endpoint, long-term study results could not be used in the NMA.

It is noteworthy that in the case of the highest ranked therapy (ixekizumab), nail assessments were performed at week 12; this suggests that assessment time within the

10–16-week range is probably not the most significant factor determining short-term nail treatment efficacy. To date, there have been very few trials evaluating nail psoriasis as a primary end-point in a placebo-controlled, prospective manner (26, 43, 47). In these RCTs long-term (week 32–52) data were indeed significantly better than short-term (week 10–16) results, and additional improvement after week 16 was between 5 and 32% of the total therapeutic result.

Thirdly, there was some diversity among the studies; for example, in terms of the presence of PsA, potentially resulting in further bias. In previous RCTs, which included patients both with and without PsA, NAPSI improvement was similar, regardless of PsA status (26, 47). This makes it rather unlikely that the presence or absence of PsA significantly influenced the results, although this cannot be ruled out entirely.

In conclusion, the results of this study have a number of implications for clinical practice and for further research.

Regarding clinical practice, the results provide additional information when choosing treatment for psoriatic patients who are candidates of systemic therapy. If clearance of nail symptoms is of considerable importance, the best option would be the IL-17 inhibitor ixekizumab, whereas ustekinumab or guselkumab are potentially less effective.

Regarding research, the results of future head-to-head comparison RCTs may be used to verify the current results. The outcome parameters and efficacy endpoints of clinical trials in the field of nail psoriasis should be standardized.

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