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REVIEW

A Comprehensive Review of Ixekizumab Efficacy in Nail Psoriasis from Clinical Trials for Moderate-to-Severe Psoriasis and Psoriatic Arthritis

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ABSTRACT

Nail psoriasis is a difficult-to-treat manifestation of psoriatic disease affecting up to 80% of patients with psoriatic arthritis (PsA) and 40–60% of patients with plaque psoriasis (PsO). Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets interleukin-17A, is approved for the treatment of patients with PsA and patients with moderate-to-severe PsO. This narrative review aims to summarize nail psoriasis data generated from IXE clinical trials in patients with PsA (SPIRIT-P1, SPIRIT-P2, and SPIRIT-H2H) and/or moderate-to-severe PsO (UNCOVER-1, -2, -3, IXORA-R, IXORA-S, and IXORA-PEDS) with an emphasis on head-to-head clinical trial data. Across numerous trials explored, IXE treatment was associated with greater improvement in resolution of nail disease versus comparators at week 24, results

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which were maintained up to and beyond week 52. Additionally, patients experienced higher rates of resolution of nail disease versus comparators at week 24 and maintained high levels of resolution up to week 52 and beyond. In both PsA and PsO, IXE demonstrated efficacy in treating nail psoriasis, and therefore may be an effective therapy option. *Trial Registration*: ClinicalTrials.gov identifier UNCOVER-1 (NCT01474512), UNCOVER-2 (NCT01597245), UNCOVER-3 (NCT01646177), IXORA-PEDS (NCT03073200), IXORA-S (NCT02561806), IXORA-R (NCT03573323), SPIRIT-P1 (NCT01695239), SPIRIT-P2 (NCT02349295), SPIRIT-H2H (NCT03151551).

Keywords: Ixekizumab; Nail psoriasis; Plaque psoriasis; Psoriatic arthritis

Key Summary Points

Nail psoriasis is a predictive factor for the development of psoriatic arthritis in patients with psoriasis and may be the first visible sign of psoriatic joint involvement.

Ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin-17A, is approved for the treatment of patients with psoriatic arthritis or moderate-to-severe psoriasis.

Numerous trials in both PsO and PsA have highlighted the efficacy of ixekizumab in clearing difficult-to-treat areas of psoriasis, including nail psoriasis.

This narrative review highlights the rapid and sustained efficacy of ixekizumab in the treatment of nail psoriasis in patients with psoriasis and/or psoriatic arthritis.

INTRODUCTION

Plaque psoriasis (PsO) is a chronic, immune-mediated, inflammatory skin condition characterized by erythematous plaques on the skin. Approximately 20–30% of patients with PsO develop psoriatic arthritis (PsA) [1, 2]. PsA is a chronic, progressive, inflammatory disease affecting the musculoskeletal system, skin, and nails. Nail psoriasis is a common and difficult-to-treat manifestation of psoriatic disease affecting 40–60% of patients with PsO and up to 80% of patients with PsA [3–5]. Nail psoriasis is a predictive factor for the development of PsA in patients with PsO and may be the first visible sign of psoriatic joint involvement. It is associated with significant physical and psychological burden in affected patients, causing pain, impairment of hand mobility, aesthetic problems, as well as an altered sense of touch [3, 6]. Nail involvement is also associated with greater disease severity and lower quality of life in patients with PsO and/or PsA [3].

Pathogenesis and Clinical Manifestations of Nail Psoriasis

The nail unit comprises the nail plate and the surrounding periungual folds, including the eponychium (proximal fold), the perionychium (lateral fold), and the hyponychium (distal fold). The nail matrix produces the keratinized nail plate while the nail bed attaches the nail plate to the distal phalanx. The hyponychium lies beneath the distal-free edge forming a natural barrier between the nail plate and nail bed [7].

Inflammation of the nail matrix or nail bed results in morphological changes characteristic of nail psoriasis. The nail unit is intimately connected to underlying bone through the enthesis network that is fused with the extensor tendon connecting the distal interphalangeal (DIP) joint [8]. Entheseal inflammation, known as enthesitis, occurs in many sites in patients with PsA, with the Achilles' tendon and plantar fascia insertions most commonly affected [8]. Nail psoriasis is often associated with enthesitis, and as a result, nail changes often precede the development of inflammation of the DIP joint [9, 10]. The spread of inflammation into the entheseal tissues and DIP joint is considered an early indicator for the presence of PsA and is

associated with increased disease severity [11]. There is evidence that sub-clinical enthesopathy in patients with PsO is a risk factor for the development of PsA [12].

Clinical manifestations of nail matrix involvement include pitting, leukonychia (white spots within the nail plate), Beau lines (transverse grooves), red spots in the lunula, and nail crumbling. Clinical manifestations of nail bed involvement include onycholysis (detachment of the nail plate from the nail bed), subungual hyperkeratosis, oil-spot discoloration, salmon patches, and splinter hemorrhages [13].

Diagnosis and Measurement of Nail Psoriasis

The assessment of nail psoriasis is based on the presence or absence of psoriatic changes in the nail. As an important predictor of disease evolution, nail psoriasis must be continuously monitored, even in the absence of skin manifestations [14]. Although nail psoriasis is an important factor in disease severity and progression, it is not evaluated by the most commonly used psoriasis assessment tool, the Psoriasis Area of Severity Index (PASI). As a result, multiple instruments have been developed to assess nail psoriasis. The most widely utilized system for measuring nail psoriasis in clinical trials is the Nail Psoriasis Severity Index (NAPSI) [15]. To calculate the NAPSI score, each nail is divided into quadrants and scored for the absence or the presence (0 or 1) of psoriasis manifestations in the nail bed and matrix [15]. Scores are summed to obtain total NAPSI nail score with a possible range of 0–160 (where a higher score indicates greater severity of nail psoriasis). NAPSI is usually used to assess the fingernails only and the toenails are often excluded (scored 0–80) [16]. For the purposes of this review and to be consistent with previously published reports, moderate-to-severe ("significant") nail psoriasis is defined as a NAPSI score $\geq$ 16 with the involvement of at least four nails. A modified version of the NAPSI (mNAPSI) includes assessment of the degree of disease severity for each nail matrix and nail bed feature in the most severely affected nail. The mNAPSI allows a comprehensive assessment of nail psoriasis, but it can be difficult to complete on a routine basis in real-life settings. An alternative measure used to evaluate psoriatic changes is the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). A PGA-F score $\geq$ 3 is indicative of moderate-to-severe nail psoriasis. Other nail scores are available to assess clinical severity of nail psoriasis, including the Nail Area Severity score, the composite nail score, and the Nail Assessment in Psoriasis and Psoriatic Arthritis tool, as well as other subtypes of NAPSI [15].

Therapies for Management of Nail Psoriasis

Traditionally, nail psoriasis is slow to resolve due to the naturally slow growth of the nail and difficult to treat as many therapies are ineffective, painful to administer, or have undesirable side effects [17]. It often persists despite control of cutaneous manifestations of psoriasis. Topical treatment of nail psoriasis is challenging due to limited penetration through the nail plate to diseased tissue and poor patient adherence. Although traditional systemic therapies may result in complete skin clearance, nail psoriasis frequently persists. Also, physicians often consider systemic therapies as inappropriate for nail psoriasis, especially in the absence of severe cutaneous psoriasis [18]. Recent emergence of biologics has revolutionized the treatment of nail psoriasis with numerous clinical trials showing improvement in nail psoriasis in patients with PsO and/or PsA following biologic treatment. However, not all biologics have demonstrated the same level of efficacy or speed in resolving nail psoriasis [19–21].

Ixekizumab

Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets interleukin-17A, is approved for the treatment of adult patients with PsA, non-radiographic axial spondyloarthritis, radiographic axial spondyloarthritis, and pediatric ($\geq$ 6 years old) and adult patients with moderate-to-severe PsO.

This narrative review will summarize nail psoriasis data generated from IXE clinical trials in patients with moderate-to-severe PsO (UNCOVER-1, UNCOVER-2, UNCOVER-3, IXORA-R, IXORA-S, and IXORA-PEDS) and patients with PsA (SPIRIT-P1, SPIRIT-P2, and SPIRIT-H2H) (Table 1), highlighting results from head-to-head trials and indirect evidence relating to IXE response rates. All phase 3 studies with ixekizumab data regarding nail psoriasis in either PsO or PsA at the time of this review were included. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Proportion of Patients with Nail Psoriasis and Severity of Nail Disease at Baseline Across IXE Studies

Across all IXE trials in PsO and PsA included in this review, a similar proportion of patients (59–73%) presented with nail psoriasis at baseline, except in IXORA-R and IXORA-PEDS (Table 2). In IXORA-R, a lower proportion of patients had nail psoriasis at baseline and it is important to note that an alternative nail psoriasis assessment tool (PGA-F) was used compared to all other clinical trials included here (Table 1). In IXORA-PEDS, a lower proportion of patients had nail psoriasis at baseline and unlike all other studies reviewed, IXORA-PEDS included only pediatric patients. Considering severity of nail disease, a similar proportion of patients presented with significant nail psoriasis (NAPSI score $\geq$ 16 with the involvement of at least four nails) across UNCOVER-3, IXORA-S and IXORA-PEDS [22–24]. In IXORA-R, 16% of IXE and 12% of guselkumab (GUS) patients had moderate-to-severe nail psoriasis as determined by a PGA-F score $\geq$ 3 [25]. Finally, an analysis of patients enrolled in SPIRIT-H2H reported that those with PsA and moderate-to-severe comorbid PsO more frequently reported nail psoriasis at baseline compared to those without moderate-to-severe PsO [IXE: 75.5% and adalimumab (ADA): 80.4% versus IXE: 65.8% and ADA: 58.9%] [26, 27].

A similar mean NAPSI score at baseline was reported across trials in PsO and PsA (Table 2). In SPIRIT-H2H, patients with PsA and concomitant moderate-to-severe PsO had numerically higher mean NAPSI score (IXE: 26.1 [standard deviation (SD) 21.6], ADA: 23.3 [SD 18.5]) at baseline compared to those without moderate-to severe PsO (IXE: 18.1 [SD 17.3], ADA: 17.8 [SD 15.4]) [26].

Changes in Nail Psoriasis Scores Over Time

PsO Trials

Early improvement of mean nail NAPSI scores with IXE treatment was noted in several trials in PsO. In the IXORA-S trial, compared to ustekinumab (UST), early mean improvements in NAPSI scores were noted with IXE treatment by week 8 (IXE: − 6.6; 95% confidence interval [CI] − 8.9, − 4.3, and UST: − 2.1; 95% CI − 4.1, − 0.1 [p = 0.002]) [22]. Similarly, in UNCOVER-3 significantly greater mean percent improvements from baseline in NAPSI scores versus comparator, etanercept (ETN), and placebo were reported by week 8 for both IXE doses [29]. In UNCOVER-2, both IXE doses had significant least square mean change from baseline in NAPSI scores versus placebo by week 4 [29, 30]. In IXORA-PEDS, mean change from baseline in NAPSI scores was significantly greater for those receiving IXE than those receiving placebo by week 12, irrespective of baseline severity of nail psoriasis [34] (Fig. 1). In IXORA-R, a significantly greater proportion of patients with moderate-to-severe nail psoriasis (PGA-F score $\geq$ 3) treated with IXE than those treated with GUS had reached clear nails or minimal nail psoriasis (PGA-F score of 0 or 1 with $\geq$ 2-point improvement) by week 24 (Table 3) [25].

NAPSI scores continued to improve up to week 52 in IXORA-S and up to week 108 in IXORA-PEDS (Fig. 1) [22, 38]. In UNCOVER-3, further mean change from baseline improvement in NAPSI scores was reported for patients with baseline and significant baseline (85.3%) nail psoriasis by week 60 (Fig. 1) [24, 29]. Long-term extension demonstrated that these improvements were maintained up to 264 weeks for patients with baseline and

Table 1 Summary of IXE trials in PsO and PsA, which include nail psoriasis evaluation

Trial	Patient population	Trial design	Duration	Phase	Comparator	Tool used to measure NP	Study aim	Primary endpoint
UNCOVER-1 NCT01474512	Mod-to-sev PsO, adult	Randomized, double-blind, placebo-controlled, multicenter	12 weeks + extension period up to 60 weeks	III	Placebo until week 12	NAPSI	To assess the safety and efficacy of IXE compared to placebo in patients with moderate-to-severe plaque psoriasis	Proportion of patients achieving PASI 75 at week 12 and proportion of patients achieving sPGA (0,1) at week 12
UNCOVER-2 NCT01597245	Mod-to-sev PsO, adult	Randomized, double-blind, placebo-controlled, multicenter	12 weeks + extension period up to 60 weeks	III	Etanercept and placebo until week 12	NAPSI	To assess the safety and efficacy of IXE compared to ETN and PBO in patients with moderate-to-severe plaque psoriasis	Proportion of patients achieving PASI 75 at week 12 and proportion of patients achieving sPGA (0,1) at week 12
UNCOVER-3 NCT01646177	Mod-to-sev PsO, adult	Randomized, double-blind, placebo-controlled, multicenter	12 weeks + extension period up to 264 weeks	III	Etanercept and placebo until week 12	NAPSI	To assess the safety and efficacy of IXE compared to ETN and PBO in patients with moderate-to-severe plaque psoriasis	Proportion of patients achieving PASI 75 at week 12 and proportion of patients achieving sPGA (0,1) at week 12

Table 1 continued

Trial	Patient population	Trial design	Duration	Phase	Comparator	Tool used to measure NP	Study aim	Primary endpoint
IXORA-S NCT02561806	Mod-to-sev PsO, adult	Multicenter, randomized, double-blind, parallel-group, head-to-head trial	52 weeks	IIIb	Ustekinumab	NAPSI	To compare the safety and efficacy of IXE with the safety and efficacy of UST through 52 weeks of treatment	Proportion of patients achieving PASI 90 at week 12
IXORA-R NCT03573323	Mod-to-sev PsO, adult	Randomized, double-blind, multicenter, parallel-group study	24 weeks	IV	Guselkumab	PGA-F	To compare skin and nail clearance and patient-reported outcomes for IXE versus GUS up to week 24	Proportion of patients achieving 100% improvement from baseline in PASI 100 at week 12
IXORA-PEDS NCT03073200	Mod-to-sev PsO, pediatric	Double-blind, placebo-controlled, randomized, multicenter	12 weeks double-blind period, 48 weeks open-label period, extension period up to 108 weeks	III	Placebo until week 12	NAPSI	To evaluate the efficacy and safety of IXE for pediatric patients with moderate-to-severe psoriasis	Proportion of patients achieving PASI 75 at week 12 and proportion of patients achieving sPGA (0,1) at week 12

Table 1 continued

Trial	Patient population	Trial design	Duration	Phase	Comparator	Tool used to measure NP	Study aim	Primary endpoint
SPIRIT-P1 NCT01695239	PsA, adult	Randomized, double-blind, placebo-controlled, and active controlled trial	24 weeks + extension period up to 156 weeks	III	Placebo and adalimumab until week 24	Fingernail NAPSI	To assess the safety and efficacy of IXE in a double-blind phase III trial enrolling patients with active PsA	Proportion of patients achieving ACR20 response at week 24
SPIRIT-P2 NCT02349295	PsA, adult Inadequate response or intolerance to TNF inhibitors	Randomized, double-blind, placebo-controlled, multicenter trial	24 weeks + extension period up to 156 weeks	III	Placebo until week 24	Fingernail NAPSI	To report efficacy and safety of IXE in patients with active PsA and previous inadequate response to tumor necrosis factor inhibitors	Proportion of patients achieving ACR20 response at week 24
SPIRIT-H2H NCT03151551	PsA, adult Inadequate response to csDMARDs	Randomized, open-label, assessor blind, multicenter, parallel-group trial	52 weeks	IIIb/IV	Adalimumab	Fingernail NAPSI	To compare efficacy and safety of IXE versus ADA in bDMARD-naïve patients as inadequate response to csDMARDs with active PsA	Proportion of patients simultaneously achieving ACR50 and PASI 100 at week 24

NP nail psoriasis, *IXE* ixekizumab, *PBO* placebo, *ADA* adalimumab, *UST* ustekinumab, *GUS* guselkumab, *ETN* etanercept, *mod-to-sev* moderate-to-severe, *TNF* tumor necrosis factor, *PsA* psoriatic arthritis, *PsO* plaque psoriasis, *NAPSI* Nail Psoriasis Severity Index, *mNAPSI* modified Nail Psoriasis Severity Index, *PGA-F* physician's global assessment fingernail, *bDMARD* biological disease-modifying anti-rheumatic drugs, *csDMARDs* conventional disease-modifying anti-rheumatic drugs, *ACR20* American College of Rheumatology 20, *ACR50* American College of Rheumatology 50, *PASI* Psoriasis Area and Severity Index, *sPGA* static Physician Global Assessment

Table 2 Patient demographics, baseline characteristics, and summary of nail psoriasis data across IXE trials in patients with PsA and/or PsO

Trial name	Treatment	Sample size	Age Mean (SD), years	Gender Female (%)	Percentage of patients with PsO	Duration since PsO diagnosis Mean (SD), years	Percentage of patients with PsA	Duration since PsA diagnosis Mean (SD), years	Percentage of patients with NP at baseline NAPSI > 0 or PGA-F > 0	NAPSI or PGA-F score at baseline Mean (SD)
UNCOVER-1, UNCOVER-2, and UNCOVER-3 (PsO) [28–31]	IXE Q4W	1165	45.4 (13.1)	32%	All patients	18.9 (12.4)	UNCOVER-3: 23.2%	NR	UNCOVER-2: 63% UNCOVER-3: 59%	24.6 (19.0)
	IXE Q2W	1169	45.1 (12.9)	35%	All patients	18.8 (12.1)	UNCOVER-3: 22.3%	NR	UNCOVER-2: 60% UNCOVER-3: 60%	25.6 (19.7)
	ETN	740	45.5 (13.3)	32%	All patients	18.5 (12.1)	UNCOVER-3: 22.5%	NR	UNCOVER-2: 64% UNCOVER-3: 62%	27.6 (20.5)
	PBO	792	46.2 (12.8)	29%	All patients	19.1 (12.1)	UNCOVER-3: 22.4%	NR	UNCOVER-2: 67% UNCOVER-3: 60%	26.3 (20.4)
IXORA-S (PsO) [22, 32]	IXE	136	43.0 (12.0)	29%	All patients	19.4 (12.0)	20.2%	NR	62%	28.3 (19.9)
	UST	166	45.4 (12.7)	24%	All patients	20.2 (11.8)	17.1%	NR	63%	24.8 (20.0)
IXORA-R (PsO) [25, 33]	IXE	520	49.0 (13.9)	35%	All patients	17.5 (13.8)	NR	NR	51%[a]	2.0 (0.9)[a]
	GUS	507	49.0 (14.9)	38%	All patients	16.3 (13.8)	NR	NR	47%[a]	1.8 (0.9)[a]

Table 2 continued

Trial name	Treatment	Sample size	Age Mean (SD), years	Gender Female (%)	Percentage of patients with PsO	Duration since PsO diagnosis Mean (SD), years	Percentage of patients with PsA	Duration since PsA diagnosis Mean (SD), years	Percentage of patients with NP at baseline NAPSI > 0 or PGA-F > 0	NAPSI or PGA-F score at baseline Mean (SD)
IXORA-PEDS	IXE	115	13.7 (3.1)	55%	All patients	4.7 (3.3)	< 1%	NR	30%	33.9 (29.5)
(PsO) [23, 34]	PBO	56	13.1 (2.8)	64%	All patients	4.7 (3.0)	0%	NR	21%	24.5 (20.9)
SPIRIT-P1	IXE Q4W	107	49.1 (10.1)	58%	94%	16.5 (13.8)	All patients	6.2 (6.4)	65%	21.3 (18.9)
(PsA) [35]	IXE Q2W	103	49.8 (12.6)	53%	92%	17.0 (14.0)	All patients	7.2 (8.0)	72%	25.0 (21.2)
	ADA	101	48.6 (12.4)	50%	96%	15.7 (12.7)	All patients	6.9 (7.5)	70%	20.9 (17.5)
	PBO	106	50.6 (12.3)	55%	96%	16.0 (13.8)	All patients	6.3 (6.9)	70%	19.8 (17.2)
SPIRIT-P2	IXE Q4W	122	52.6 (13.6)	48%	97%	15.7 (12.3)	All patients	11.0 (9.6)	73%	20.5 (20.0)
(PsA) [36]	IXE Q2W	123	51.7 (11.9)	59%	92%	16.5 (13.0)	All patients	9.9 (7.4)	60%	21.0 (22.0)
	PBO	118	51.5 (10.4)	53%	92%	15.3 (12.6)	All patients	9.2 (7.3)	62%	18.7 (18.8)

Table 2 continued

Trial name	Treatment	Sample size	Age Mean (SD), years	Gender Female (%)	Percentage of patients with PsO	Duration since PsO diagnosis Mean (SD), years	Percentage of patients with PsA	Duration since PsA diagnosis Mean (SD), years	Percentage of patients with NP at baseline NAPSI > 0 or PGA-F > 0	NAPSI or PGA-F score at baseline Mean (SD)
SPIRIT-H2H (PsA) [26, 37]	IXE	283	47.5 (12.0)	43%	All patients 17% (mod-to-sev PsO)	16.1 (13.1)	All patients	6.6 (7.4)	68%	19.7 (18.5)
	ADA	283	48.3 (12.3)	47%	All patients 18% (mod-to-sev PsO)	14.7 (12.6)	All patients	5.9 (6.4)	63%	19.1 (16.3)

NP nail psoriasis, *IXE* ixekizumab, *IXE Q4W* ixekizumab every 4 weeks, *IXE Q2W* ixekizumab every 2 weeks, *PBO* placebo, *ADA* adalimumab, *UST* ustekinumab, *GUS* guselkumab, *ETN* etanercept, *mod-to-sev* moderate-to-severe, *PsA* psoriatic arthritis, *PsO* plaque psoriasis, *NAPSI* Nail Psoriasis Severity Index, *PGA-F* patient global assessment fingernail, *SD* standard deviation, *NR* not reported

[a]PGA-F was used to assess nail psoriasis severity

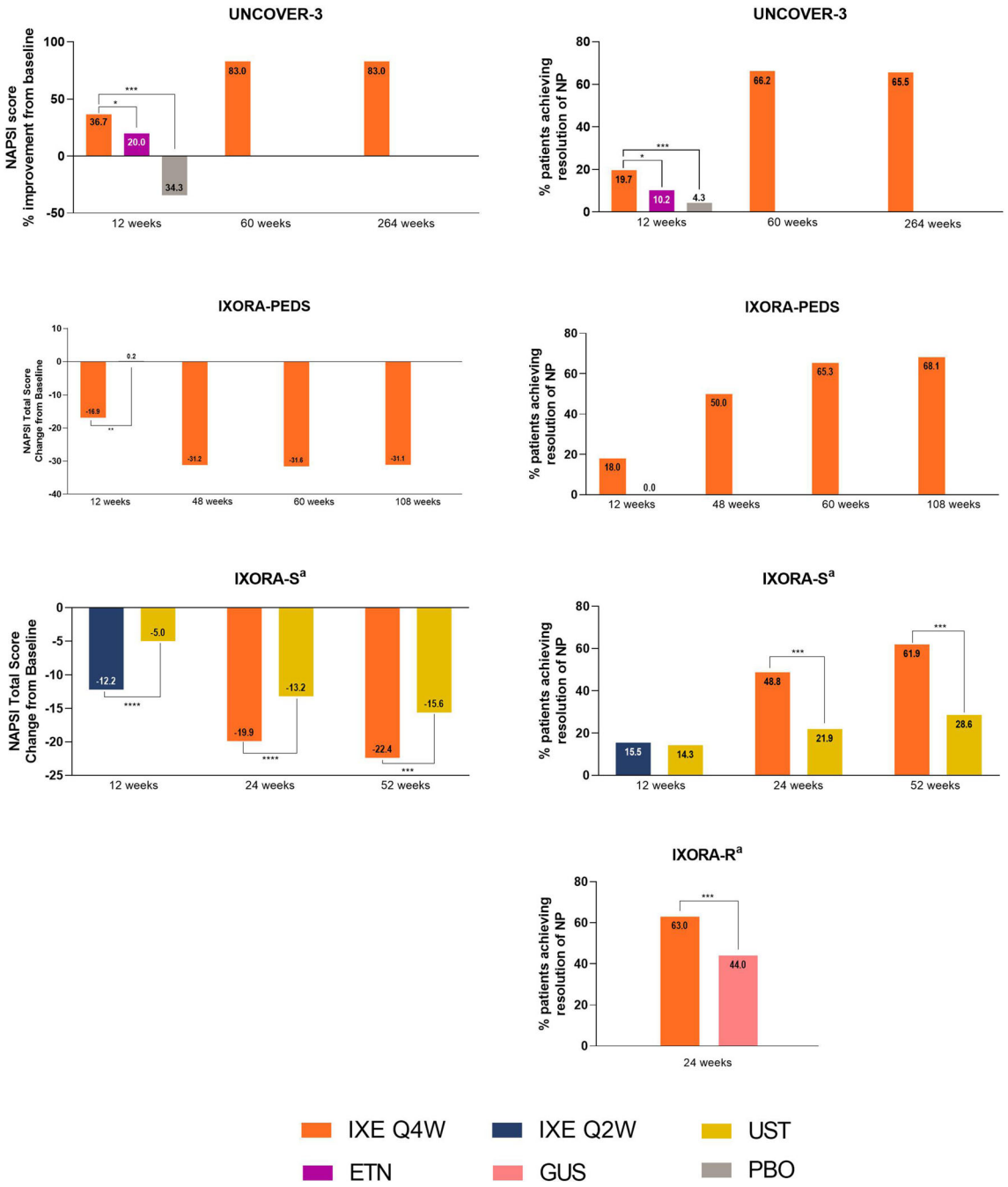

Fig. 1 Summary of nail psoriasis data across IXE trials in patients with PsO with concomitant nail psoriasis at baseline. Note: Where available, additional IXE Q2W data are included in supplemental figure 1. [a]In IXORA-S and IXORA-R, patients received IXE Q2W for the first 12 weeks of treatment before switching to IXE Q4W. *IXE Q4W* ixekizumab every 4 weeks, *IXE Q2W* ixekizumab every 2 weeks, *PsO* plaque psoriasis, *NP* nail psoriasis, *ETN* etanercept, *PBO* placebo, *UST* ustekinumab, *GUS* guselkumab, *NAPSI* Nail Psoriasis Severity Index. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$ significant versus comparator

significant baseline (87.6%) nail psoriasis (Fig. 1) [24].

Additionally, findings from IXORA-PEDS demonstrated improvements in nail psoriasis of

Table 3 Summary of nail psoriasis data across IXE trials in patients with PsA and/or PsO with concomitant "significant" or moderate-to-severe nail psoriasis at baseline

Trial name	Definition of significant or mod-to-sev NP	Treatment	Percentage of patients with significant/mod-to-sev NP at baseline[b]	NAPSI score at baseline Mean (SD)	Percentage of patients achieving complete resolution of NP			Nail psoriasis improvement (Change from baseline)		
					W12	W24	W52	W12	W24	W52
UNCOVER-3 [24, 45]	Included patients with significant NP defined as a NAPSI score ≥ 16 with the involvement of at least four nails	IXE Q4W	61.2%	39 (16)	NR	34%	NR	40%	NR	NR
		IXE Q2W	NR	38 (16)	NR	NR	NR	39%	NR	NR
		ETN	NR	37 (18)	NR	NR	NR	28%	NR	NR
		PBO	NR	37 (17)	NR	NR	NR	− 4.7%	NR	NR
IXORA-S [22]	Included patients with significant NP defined as a NAPSI score ≥ 16 with the involvement of at least four nails	IXE	64.3%	NR	NR	NR	57.4%***	NR	NR	NR
		UST	60.0%	NR	NR	NR	17.5%	NR	NR	NR
IXORA-R[a] [25]	Included patients with moderate-to-severe NP defined as a PGA-F score ≥ 3	IXE	31.4%	NR	NR	52%**	NR	NR	75%* Achieved PGA-F score of 0 or 1 with ≥ 2-point improvement	NR
		GUS	24.7%	NR	NR	31%	NR	NR	54% Achieved PGA-F score of 0 or 1 with ≥ 2-point improvement	NR

Table 3 continued

Trial name	Definition of significant or mod-to-sev NP	Treatment	Percentage of patients with significant/mod-to-sev NP at baseline[b]	NAPSI score at baseline Mean (SD)	Percentage of patients achieving complete resolution of NP			Nail psoriasis improvement (Change from baseline)		
					W12	W24	W52	W12	W24	W52
IXORA-PEDS [23]	Included patients with significant NP defined as a NAPSI score $\geq$ 16 with the involvement of at least four nails	IXE	58.8%	52.0 (25.8)	15%	40%	NR	NR	NR	NR

NP nail psoriasis, *IXE* ixekizumab, *PBO* placebo, *UST* ustekinumab, *GUS* guselkumab, *mod-to-sev* moderate-to-severe, *W* week, *PsA* psoriatic arthritis, *PsO* plaque psoriasis, *NAPSI* Nail Psoriasis Severity Index, *PGA-F* Patient Global Assessment Fingernail, *SD* standard deviation, *NR* not reported

[a]PGA-F was used to assess nail psoriasis severity

[b]All values represent the percentage of patients with significant/moderate-to-severe baseline nail psoriasis of all patients with baseline nail psoriasis

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

****$p < 0.0001$ significant versus comparator

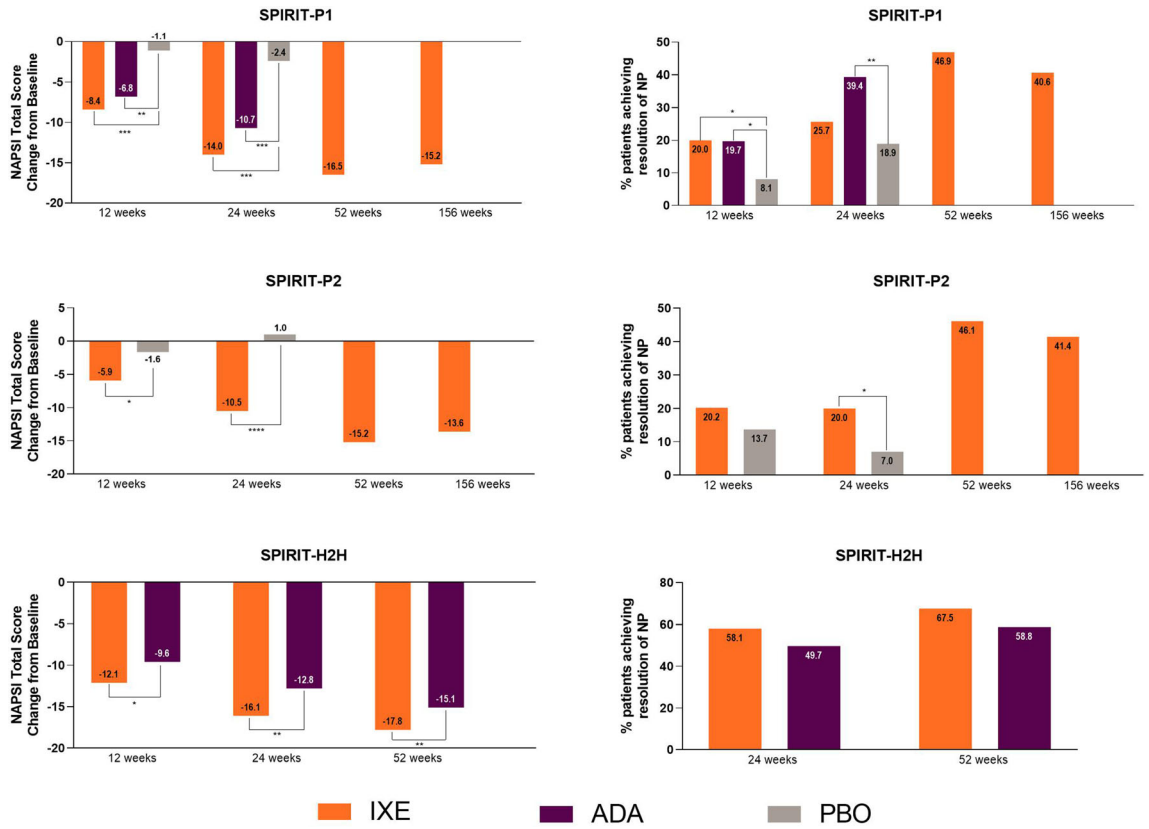

Fig. 2 Summary of nail psoriasis data across IXE trials in patients with PsA with concomitant nail psoriasis at baseline (NAPSI > 0). Note: At 52 weeks, only extension period population nail psoriasis data has been reported, therefore only the extension period population data has been presented at this timepoint. Only IXE Q4W data have been included here. Where available, IXE Q2W data are included in supplemental figure 2. *IXE* ixekizumab, *IXE Q4W* ixekizumab every 2 weeks, *IXE Q2W* ixekizumab every 2 weeks, *NP* nail psoriasis, *PsA* psoriatic arthritis, *PBO* placebo, *ADA* adalimumab, *NAPSI* Nail Psoriasis Severity Index. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$ significant versus comparator

both the nail bed and nail matrix regions with only marginally slower responses observed in the nail matrix compared to the nail bed [23]. In UNCOVER-3, similar findings were reported in adult patients with moderate-to-severe psoriasis [24].

PsA Trials

In SPIRIT-P1, significant improvement in fingernail NAPSI scores with IXE was noted as early as week 12 [35, 37] (Fig. 2). The primary endpoint [proportion of patients achieving American College of Rheumatology (ACR) 20 response] of SPIRIT-P1 and SPIRIT-P2 was evaluated at week 24, and fingernail NAPSI score change from baseline was significantly greater for IXE patients compared to placebo at this timepoint [35, 36]. Likewise, the primary endpoint (proportion of patients simultaneously achieving ACR50 and PASI 100) was measured at week 24 in SPIRIT-H2H, and fingernail NAPSI score change from baseline at this timepoint was significantly greater for IXE compared to ADA.

Further improvement from baseline in nail psoriasis scores was reported at week 52 in SPIRIT-P1, SPIRIT-P2, and SPIRIT-H2H [37, 39, 40] (Fig. 2). Long-term extension of SPIRIT-P1 and SPIRIT-P2 studies demonstrated that improvement in fingernail NAPSI scores is

maintained up to 156 weeks in patients with PsA on IXE treatment [41, 42] (Fig. 2). For those with concomitant moderate-to-severe PsO in SPIRIT-H2H, change from baseline was significantly greater at week 40 and similar at week 52 for IXE-treated patients compared to those treated with ADA (IXE: − 21.9 and ADA: − 20.9, $p = 0.583$) [43].

Resolution of Nail Psoriasis with IXE in PsA and PsO Trials

Due to the significant quality of life burden and impairment of physical functioning associated with nail disease, complete clearance is arguably the most important treatment goal from both the patient's and clinician's perspective [4]. Additionally, it has been postulated that complete resolution of nail disease may be important in preventing the future development of PsA [14, 16]. Across all IXE clinical trials included in this review, a high proportion of patients with PsO and/or PsA achieved complete resolution of nail disease irrespective of severity at baseline (Figs. 1 and 2, Table 3).

PsO Trials

Integrated analysis from all three UNCOVER studies in PsO demonstrated rapid benefit of IXE treatment. A significantly greater proportion of patients treated with IXE achieved complete clearance of nail psoriasis compared to ETN at week 12 (IXE every four weeks: 14.8%, IXE every two weeks: 16.6%, ETN: 10.3%, and placebo [PBO]: 4.9% [$p < 0.001$ versus PBO, $p \leq 0.01$ versus ETN]) [28]. In UNCOVER-3, the percentage of IXE-treated patients who achieved complete clearance of nail psoriasis increased from week 12 to week 60 and was maintained up to week 264 (Fig. 1)[44]. Similarly, 59.1 and 65.5% of patients with significant baseline nail psoriasis had achieved complete clearance of nail psoriasis at week 60 and week 264, respectively, demonstrating long-term efficacy of IXE in clearing nail psoriasis [24].

In IXORA-S, significantly more patients treated with IXE achieved complete nail clearance (IXE: 31.0% versus UST: 16.2%; $p = 0.02$) compared to UST by week 16 and by week 20 (IXE: 25.9% versus UST: 9.5%; $p = 0.03$) for patients with significant nail psoriasis [22]. By week 52, the majority of patients with baseline nail psoriasis and significant baseline nail psoriasis had achieved complete nail resolution [22] (Fig. 1, Table 3). In IXORA-R, a significantly greater proportion of patients with baseline nail psoriasis and significant baseline nail psoriasis achieved resolution at week 24 compared to GUS [25] (Fig. 1).

A numerically higher proportion of pediatric patients in IXORA-PEDS had achieved complete resolution of nail disease by week 12 with IXE treatment compared with placebo, regardless of baseline nail disease severity, and complete resolution of nail disease was maintained up to week 108 (Fig. 2) [23, 34, 38].

PsA Trials

In PsA trials SPIRIT-P2 and SPIRIT-H2H, a significantly greater proportion of patients had achieved complete resolution of nail disease with IXE treatment compared to placebo or active comparator at week 24 [35, 36, 43] (Fig. 2). In the SPIRIT-P1 study, at week 12, significantly more patients achieved complete nail clearance with IXE compared to placebo [35]. Analysis of SPIRIT-H2H reported that significantly greater numbers of patients with PsA and moderate-to-severe PsO treated with IXE (75.7%) achieved complete resolution of nail disease compared to comparator, ADA (51.2%, $p = 0.035$) at week 24 [26]. For those patients without moderate-to-severe PsO, the proportion of nail clearance was similar for both IXE- and ADA-treated patients at week 24 (53.9% versus 49.3%, $p = 0.480$) [26, 27].

By week 52, a similar number of patients across SPIRIT-P1 and SPIRIT-P2 achieved complete resolution of nail disease with IXE treatment (Fig. 2) [39, 40]. In SPIRIT-H2H, patients receiving IXE that achieved complete resolution of nail disease at 52 weeks was not statistically different from those receiving ADA [37] (Fig. 2). A higher percentage of patients with PsA and comorbid moderate-to-severe PsO treated with IXE achieved complete resolution of nail disease by week 52 than those treated with ADA (IXE: 78.4%, ADA: 68.3%; $p = 0.444$) [26]. Long-term

extension studies demonstrated that a high proportion of patients maintain complete nail clearance up to 156 weeks, with continuous IXE treatment [41, 42] (Fig. 2).

Indirect Comparative Data on Nail Psoriasis

Three recent network meta-analyses (NMA) have evaluated the comparative efficacy of approved biologics and small molecules in treating nail psoriasis [19–21]. Using a Bayesian NMA, Szebényi et al. reported that in the short-term (10–16 weeks) IXE every four weeks ranked highest for NAPSI percentage improvement, followed by IXE every two weeks [20]. Reich et al. reported the probability for complete resolution of nail disease at week 24–26 in patients with moderate-to-severe PsO and concomitant baseline nail psoriasis, which was highest for IXE (46.5%), followed by brodalumab (37.0%), ADA (28.3%), GUS (27.7%), UST (20.8%), and infliximab (0.8%) [21]. Similarly, Huang et al. reported from an NMA that IXE presented the greatest improvement in nail psoriasis at 24–-26 weeks. Additionally, IXE ranked the best amongst five treatments (IXE, GUS, ADA, PBO, and UST) for complete resolution of nail psoriasis [19].

CONCLUSIONS

Numerous trials in both PsO and PsA have highlighted the efficacy of IXE in clearing nail PsO, which often precedes the development of PsA and may be the earliest visible sign of psoriatic joint involvement [25, 46, 47]. This review highlights the rapid and sustained efficacy of IXE in the treatment of nail psoriasis in patients with PsO and/or PsA.

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