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Clinical science

Enthesitis in patients with psoriatic arthritis treated with secukinumab or adalimumab: a post hoc analysis of the EXCEED study

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Abstract

Objectives: To evaluate enthesitis treatment response, including time to resolution and data from multiple enthesitis instruments, in patients with PsA treated with secukinumab or adalimumab for 52 weeks.

Methods: In this post hoc analysis of the EXCEED study, patients receiving secukinumab 300 mg or adalimumab 40 mg per the label were grouped by presence or absence of baseline enthesitis based on the Leeds Enthesitis Index (LEI) and the Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC). Efficacy was assessed according to several enthesitis-related instruments using non-responder imputation for the achievement of enthesitis resolution (LEI/SPARCC = 0), Kaplan–Meier analysis for time to resolution, and as-observed data for other outcomes.

Results: Enthesitis was present at baseline in 498 of 851 patients (58.5%) as assessed by LEI and in 632 of 853 patients (74.1%) as assessed by SPARCC. Patients with baseline enthesitis generally presented with greater disease activity. Similar proportions of patients receiving secukinumab or adalimumab achieved resolution of LEI and SPARCC at weeks 24 (secukinumab: LEI/SPARCC, 49.6%/45.8%; adalimumab: LEI/SPARCC, 43.6%/43.5%) and 52 (secukinumab: LEI/SPARCC, 60.7%/53.2%; adalimumab: LEI/SPARCC, 55.3%/51.4%), with comparable mean time to enthesitis resolution. Improvements were similar for both drugs at individual enthesitis sites. Resolution of enthesitis with secukinumab or adalimumab was associated with improvements in quality of life at week 52.

Conclusion: Secukinumab and adalimumab showed similar efficacy, including time to resolution, with respect to resolution of enthesitis. Inhibition of IL-17 with secukinumab reduced clinical enthesitis similarly to TNF- α inhibition.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov), NCT02745080

Keywords: enthesitis, PsA, secukinumab, IL-17 inhibitor, biologics, bDMARDs, head-to-head

Rheumatology key messages

- PsA patients with enthesitis had greater disease activity, pain and psoriasis than those without enthesitis.
- Secukinumab and adalimumab led to similar achievement of enthesitis resolution overall and at individual sites.
- Patients taking either drug displayed similar time to enthesitis resolution, irrespective of baseline enthesitis severity.

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Introduction

Enthesitis is an early and characteristic musculoskeletal manifestation of PsA that is associated with greater disease activity and reduced quality of life [1, 2]. Defined as inflammation of the entheses—where a tendon or ligament inserts into bone—enthesitis has been proposed to be the primary manifestation of PsA [3, 4]. Clinical enthesitis occurs in around 35–50% of patients with PsA [1, 5]; these patients experience significantly higher disease burden and greater erosive damage than patients without enthesitis [6, 7]. Resolution of enthesitis is an important clinical outcome used to assess treatment response among patients with PsA and has been associated with improvements in other clinical outcomes [8, 9].

The European Alliance of Associations for Rheumatology (EULAR; formerly the European League Against Rheumatism) guidelines recommend biologic DMARDs (bDMARDs) for patients with enthesitis and an inadequate response to or intolerance of NSAIDs. However, no guidance on specific bDMARDs is offered [10]. Secukinumab, a fully human monoclonal antibody that selectively neutralizes IL-17A, has shown early and sustained efficacy and safety in treating PsA [11] and has specifically been shown to reduce enthesitis in patients with PsA in a pooled analysis of four phase 3 trials [12]. Adalimumab, a TNF inhibitor, is approved and widely used for the treatment of PsA and remains a mainstay of PsA treatment [10, 13].

In the EXCEED head-to-head, double-blind study (NCT02745080) comparing secukinumab with adalimumab in patients with PsA and active psoriasis, the primary endpoint of superiority of American College of Rheumatology 20% improvement criteria (ACR20) response at week 52 for secukinumab *vs* adalimumab was not met, although similar efficacy was observed across a range of musculoskeletal endpoints, including resolution of enthesitis at week 52 [14]. However, a detailed analysis of enthesitis was not conducted. This study aims to provide detail on enthesitis treatment response, including temporal response and site-specific enthesitis data along with additional enthesitis assessments, in patients with PsA treated with secukinumab or adalimumab over 52 weeks in EXCEED.

Methods

Study design and patient data

EXCEED was a multicentre, randomized, double-blind, active-controlled, parallel-group, phase 3 trial that evaluated the efficacy and safety of secukinumab *vs* adalimumab in treating patients with PsA [14]. Eligible patients had a diagnosis of PsA per the Classification Criteria for Psoriatic Arthritis (CASPAR) and active plaque psoriasis or nail changes consistent with psoriasis and were naïve to bDMARDs. Patients were randomized 1:1 to secukinumab 300 mg or adalimumab 40 mg per the label; to maintain blinding, both groups received placebo injections to ensure that a consistent number of injections were administered per visit. The EXCEED study was conducted at 187 centres in 26 countries and was approved by the institutional review board or independent ethics committee at each participating institution and conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent before starting any study-related procedures.

In this post hoc analysis, patient data from EXCEED were grouped by presence or absence of baseline enthesitis based on the Leeds Enthesitis Index (LEI) and the Spondyloarthritis

Research Consortium of Canada Enthesitis Index (SPARCC). All enrolled patients were included in this post hoc analysis. The study was approved by the central institutional review board Chesapeake IRB (now Advarra; IRB no. 00023362).

Outcomes and assessments

Demographics and baseline disease characteristics of all four enthesitis groups (LEI/SPARCC enthesitis or no enthesitis) were summarized. The efficacy of secukinumab *vs* adalimumab through week 52 was evaluated among the enthesitis subset according to several outcome measures of enthesitis response, including median time to resolution of LEI/SPARCC enthesitis score in patients receiving secukinumab or adalimumab; LEI and SPARCC mean total score by visit; LEI and SPARCC mean change from baseline at weeks 24 and 52; resolution of enthesitis as measured by LEI (LEI=0) or SPARCC (SPARCC=0) at weeks 24 and 52; and relapse of clinical enthesitis after a first resolution of enthesitis at weeks 24 and 52. Prevention of enthesitis among patients with no enthesitis at baseline (LEI=0 or SPARCC=0) was determined by the proportion of patients with no new LEI or SPARCC findings through week 52.

Resolution of LEI or SPARCC enthesitis at week 52 and time to resolution of enthesitis was also assessed by number of involved entheses at baseline. For these analyses, LEI severity was based on the following cutoffs [15]: LEI >0 to <2, LEI 2 to ≤3, and LEI >3 to ≤6; SPARCC severity levels were defined as SPARCC >0 to <3, SPARCC 3 to ≤6, and SPARCC >6 to ≤16. Site-level enthesitis distribution at baseline and resolution at weeks 12, 24 and 52 were evaluated for all SPARCC and LEI enthesitis sites among patients with baseline enthesitis as measured by SPARCC or LEI.

Improvement in quality of life was determined by the achievement of patient-reported outcome (PRO) responses per week-52 enthesitis resolution status (among patients with and without enthesitis at week 52). Health-related quality of life (HRQOL) improvements were assessed by the achievement of a minimal clinically important difference (MCID) of ≥2.5 in the raw 36-Item Short Form Health Survey physical component summary (SF-36 PCS; scale, 0–100) as established in rheumatoid arthritis [16]. Physical function was evaluated by achievement of the MCID of ≥0.35 in the Health Assessment Questionnaire–Disability Index (HAQ-DI; scale, 0–3) [17].

Statistical analysis

Time to resolution of enthesitis, both overall and by number of enthesitis-affected joints at baseline, was assessed using Kaplan–Meier analysis. Non-responder imputation was used to assess achievement of enthesitis resolution. Descriptive statistics were provided for other endpoints using an observed-case approach. No statistical hypothesis tests for superiority or equivalence with respect to enthesitis response were planned in the EXCEED study protocol, and none were performed in this exploratory, hypothesis-generating, secondary analysis.

Results

Demographics and baseline characteristics

This post hoc analysis included all patients from the EXCEED study who completed 52 weeks of treatment ($n=853$). Of

851 total patients assessed by LEI, 498 (58.5%) had enthesitis at baseline, and 353 (41.5%) did not; of 853 total patients assessed by SPARCC, 632 (74.1%) had enthesitis at baseline, and 221 (25.9%) did not.

Demographics and baseline disease characteristics, including the proportion of patients with baseline CRP ≥ 10 mg/L, were balanced in the LEI/SPARCC enthesitis subsets, although a higher proportion of all patients with enthesitis were women *vs* those with no enthesitis (Table 1). The proportion of female and male patients was similar in both the secukinumab and adalimumab treatment groups overall. Patients with baseline enthesitis tended to present with greater disease activity, including higher tender joint counts, higher Psoriasis Area and Severity Index score, higher PsA pain visual analogue scale scores and worse physical function, *vs* patients without enthesitis. Patients with enthesitis had higher body mass index than those without, although the distribution of body mass index was similar across treatment groups. The distribution of enthesitis severity at baseline was similar between groups of patients receiving either secukinumab or adalimumab; each treatment group contained similar proportions of patients grouped by level of baseline enthesitis site involvement (Supplementary Table S1, available at *Rheumatology* online).

Efficacy among LEI and SPARCC subsets

Both secukinumab and adalimumab resulted in similar improvements in enthesitis as measured by the mean change from baseline in LEI and SPARCC enthesitis counts at weeks 24 and 52 (Fig. 1A). At week 24, mean (s.d.) change from baseline in LEI and SPARCC enthesitis counts for patients receiving secukinumab was -1.6 (1.6) and -3.3 (3.5), respectively; LEI and SPARCC improvement from baseline for patients receiving adalimumab was -1.6 (1.6) and -3.1 (3.5), respectively. These improvements were sustained through week 52, when mean (s.d.) change from baseline in LEI and SPARCC enthesitis counts for patients receiving secukinumab was -1.8 (1.6) and -3.6 (3.2), respectively; LEI and SPARCC improvement for patients receiving adalimumab was -2.1 (1.7) and -3.9 (3.8), respectively. Similar proportions of patients in both treatment groups achieved resolution of LEI and SPARCC at weeks 24 and 52 (Fig. 1B). By week 24, 49.6% and 45.8% of patients receiving secukinumab and 43.6% and 43.5% of patients receiving adalimumab achieved resolution of LEI and SPARCC enthesitis, respectively. These results were extended through week 52, when 60.7% and 53.2% of patients receiving secukinumab and 55.3% and 51.4% of patients receiving adalimumab achieved resolution of LEI and SPARCC enthesitis, respectively. Additionally, change from baseline in number of affected entheses by visit followed similar trajectories for patients receiving either drug (Supplementary Fig. S1, available at *Rheumatology* online).

The time to enthesitis resolution was comparable for both drugs. Similar median (95% CI) times to resolution of enthesitis were observed between groups of patients receiving secukinumab and adalimumab, with overlapping 95% CIs (Fig. 2, Supplementary Fig. S2, available at *Rheumatology* online). Time to LEI resolution was 85 (57–113) days for patients receiving secukinumab and 85 (57–86) days for patients receiving adalimumab. Time to SPARCC resolution was 113 (85–169) days for patients receiving secukinumab and 88 (85–114) days for patients receiving adalimumab. Additionally, achievement of enthesitis resolution was similar between treatment groups irrespective of disease severity, as defined

above by number of LEI or SPARCC sites involved (Fig. 3). However, patients in either treatment group with a greater number of involved joints at baseline experienced the longest time to response among all subgroups.

The proportion of patients who experienced relapse after achieving initial resolution of enthesitis was low across both treatments (Supplementary Table S2, available at *Rheumatology* online). Similarly, both drugs prevented the development of enthesitis through week 52 among patients who had no enthesitis at baseline (Supplementary Fig. S3, available at *Rheumatology* online).

Site-specific enthesitis distribution and treatment response

Distribution of enthesitis sites at baseline was well balanced among patients across the two treatment groups and by upper and lower extremity involvement (Supplementary Fig. S4, available at *Rheumatology* online). Patients randomized to secukinumab most frequently experienced baseline enthesitis of the lateral epicondyle (33.0%) and greater trochanter (32.8%); those randomized to adalimumab most frequently had baseline enthesitis of the lateral epicondyle (39.3%) and the Achilles tendon insertion into the calcaneum (38.6%).

By week 12, a high proportion of patients in both treatment groups achieved similar resolution of enthesitis at the level of individual entheses across all SPARCC sites (Fig. 4), with sustained improvement through week 52. Secukinumab and adalimumab resulted in similar improvements in enthesitis of the medial femoral condyle through week 52, which is measured by LEI but not by SPARCC.

Improvements in HRQOL by enthesitis status at week 52

Finally, we assessed the efficacy of secukinumab and adalimumab treatment on HRQOL and physical function by enthesitis status (enthesitis resolution or no enthesitis resolution as measured by LEI and SPARCC) at week 52 (Fig. 5). Secukinumab and adalimumab resulted in similar achievement of SF-36 PCS improvement ≥ 2.5 and HAQ-DI improvement ≥ 0.35 at week 52 within enthesitis status groups. For both drugs, the greatest improvements occurred among patients who achieved enthesitis resolution.

Discussion

In this post hoc analysis of the EXCEED study, secukinumab and adalimumab performed similarly in patients with enthesitis at baseline, as measured by LEI >0 or SPARCC >0 . Enthesitis was evenly distributed across both treatment groups, although patients with baseline enthesitis presented with greater disease activity and pain than those without, consistent with the patient population enrolled in the previous FUTURE trials [15]. Additionally, enthesitis was not evenly distributed by sex; a greater proportion of patients in either treatment group who had enthesitis at baseline were women compared with patients without enthesitis. This observation potentially reflects the greater disease burden, presentation of peripheral arthritis and limitations in function among women *vs* men with PsA observed in the real world [18–20]. In a previous post hoc analysis of EXCEED, women appeared to achieve numerically higher musculoskeletal responses with secukinumab than with adalimumab, while men had similar

Table 1. Demographics and baseline disease characteristics of patients grouped by LEI and SPARCC status

Characteristic	By LEI status				By SPARCC status			
	Secukinumab, 300 mg		Adalimumab, 40 mg		Secukinumab, 300 mg		Adalimumab, 40 mg	
	(n = 424)		(n = 427)		(n = 426)		(n = 427)	
	LEI enthesitis (n = 234)	No LEI enthesitis (n = 190)	LEI enthesitis (n = 264)	No LEI enthesitis (n = 163)	SPARCC enthesitis (n = 301)	No SPARCC enthesitis (n = 125)	SPARCC enthesitis (n = 331)	No SPARCC enthesitis (n = 96)
Age, mean (s.d.), years	49.0 (12.5)	47.7 (12.2)	49.5 (12.7)	49.5 (12.0)	48.8 (12.5)	47.6 (12.2)	49.6 (12.7)	49.0 (11.8)
Male, n (%)	95 (40.6)	112 (58.9)	131 (49.6)	98 (60.1)	131 (43.5)	77 (61.6)	165 (49.8)	64 (66.7)
BMI, mean (s.d.), kg/m ²	29.6 (6.4)	27.6 (5.3)	29.4 (5.6)	28.1 (5.4)	29.2 (6.2)	27.7 (5.6)	29.2 (5.6)	27.7 (5.0)
CRP ≥10 mg/l, n (%)	68 (29.1)	62 (32.6)	80 (30.3)	48 (29.4)	90 (29.9)	41 (32.8)	100 (30.2)	28 (29.2)
Presence of dactylitis, n (%)	73 (31.2)	57 (30.0)	83 (31.4)	54 (33.1)	92 (30.6)	38 (30.4)	112 (33.8)	25 (26.0)
TJC78, mean (s.d.)	21.9 (15.3)	15.9 (10.2)	23.6 (16.0)	15.7 (11.2)	21.5 (14.9)	14.3 (9.0)	22.8 (15.6)	13.2 (8.3)
SJC76, mean (s.d.)	9.7 (7.4)	9.7 (7.2)	10.9 (8.4)	9.0 (6.8)	9.7 (1.5)	9.8 (6.9)	10.8 (8.5)	8.2 (4.8)
PASI, mean (s.d.)	6.5 (9.1)	5.5 (6.2)	6.3 (7.5)	4.6 (6.3)	6.1 (8.1)	6.0 (7.6)	6.0 (7.3)	4.5 (6.0)
Patient global assessment (VAS 0–100), mean (s.d.)	64.8 (18.8)	63.0 (20.8)	63.5 (20.2)	59.1 (21.4)	64.4 (19.2)	63.0 (20.7)	62.0 (20.8)	61.4 (20.8)
PsA Pain (VAS 0–100), mean (s.d.)	59.9 (23.1)	56.7 (23.9)	60.3 (20.9)	54.1 (24.2)	59.2 (23.6)	57.0 (23.3)	59.1 (21.8)	53.7 (24.0)
HAQ-DI, mean (s.d.)	1.36 (0.60)	1.15 (0.66)	1.32 (0.61)	1.09 (0.67)	1.33 (0.61)	1.12 (0.68)	1.29 (0.62)	1.02 (0.68)
Time since PsA diagnosis, mean (s.d.), years	5.2 (7.4)	5.0 (7.9)	5.5 (6.8)	5.9 (8.1)	5.3 (7.5)	4.7 (7.9)	5.8 (7.1)	5.1 (7.9)

HAQ-DI: HAQ-Disability Index; LEI: Leeds Enthesitis Index; PASI: Psoriasis Area and Severity Index; SJC76: swollen joint count of 76 joints; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index; TJC78: tender joint count of 78 joints; VAS: visual analogue scale.

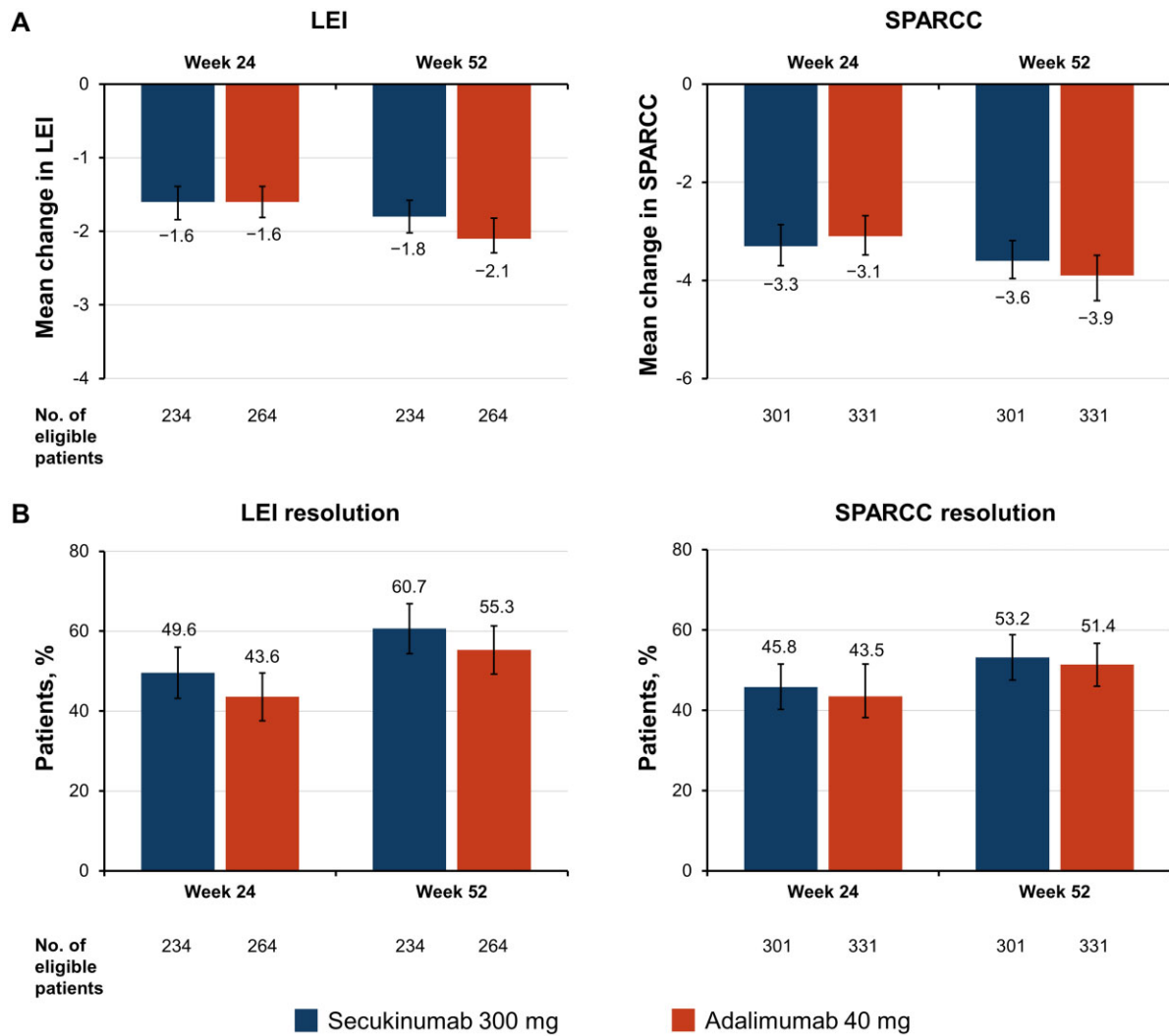


Figure 1. Enthesitis improvements at weeks 12 and 24 as determined by (A) mean change from baseline in LEI and SPARCC enthesitis counts and (B) the proportion of patients achieving LEI or SPARCC resolution (non-responder imputation). Error bars represent 95% CIs. LEI: Leeds Enthesitis Index; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index

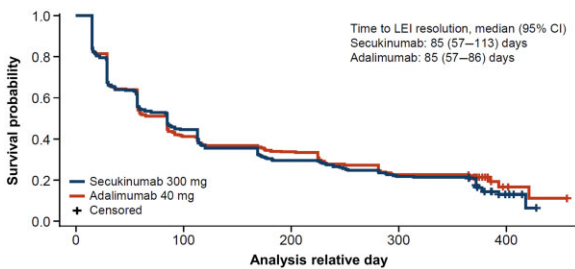


Figure 2. Kaplan–Meier estimate of time to first resolution of LEI enthesitis up to week 52. LEI: Leeds Enthesitis Index

musculoskeletal responses with both drugs [21]. Although both treatment groups here had a similar proportion of female patients, no subgroup analysis of enthesitis resolution by sex was performed in this study. Future analyses of the effects of sex on enthesitis treatment response are needed.

Although the overall primary outcome of superiority of ACR20 response for secukinumab *vs* adalimumab was not met in EXCEED [14], this post hoc analysis indicates that secukinumab and adalimumab resulted in similar improvements in

enthesitis. Both drugs showed similar time to response with respect to resolution of enthesitis, both overall and by severity at baseline. Efficacy according to number of affected entheses at baseline was similar for both drugs, although achievement of resolution with either drug tended to be lower among patients with greater baseline severity of enthesitis.

One potential confounder with assessing enthesitis severity by number of sites, especially among patients with large numbers of affected entheses, is the possible concomitant or differential diagnosis of fibromyalgia [22–24], which may influence the enthesitis count and limit the apparent treatment response. More broadly, differential diagnoses such as fibromyalgia, chronic widespread pain, osteoarthritis, mechanically triggered pain and obesity contribute to the challenge of clinical assessment of enthesitis, as clinical assessment of tenderness does not discriminate by cause [1, 24]. Using fibromyalgia or chronic widespread pain as exclusion criteria could mitigate this issue in clinical trials; however, real-world implications remain for patients. As musculoskeletal ultrasound or magnetic resonance imaging could provide a more sensitive and specific measure of enthesitis and other PsA-related inflammatory changes compared with clinical assessment alone, such

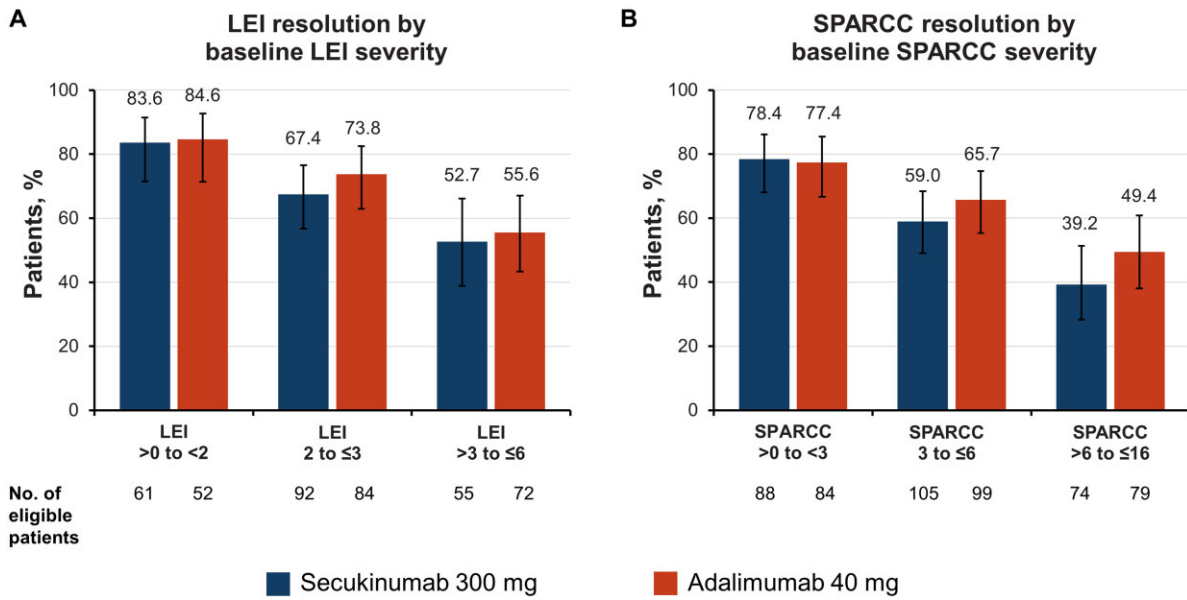


Figure 3. Proportion of patients achieving resolution of enthesitis at week 52 by baseline (A) LEI and (B) SPARCC enthesitis severity. Error bars represent 95% CIs. LEI: Leeds Enthesitis Index; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index

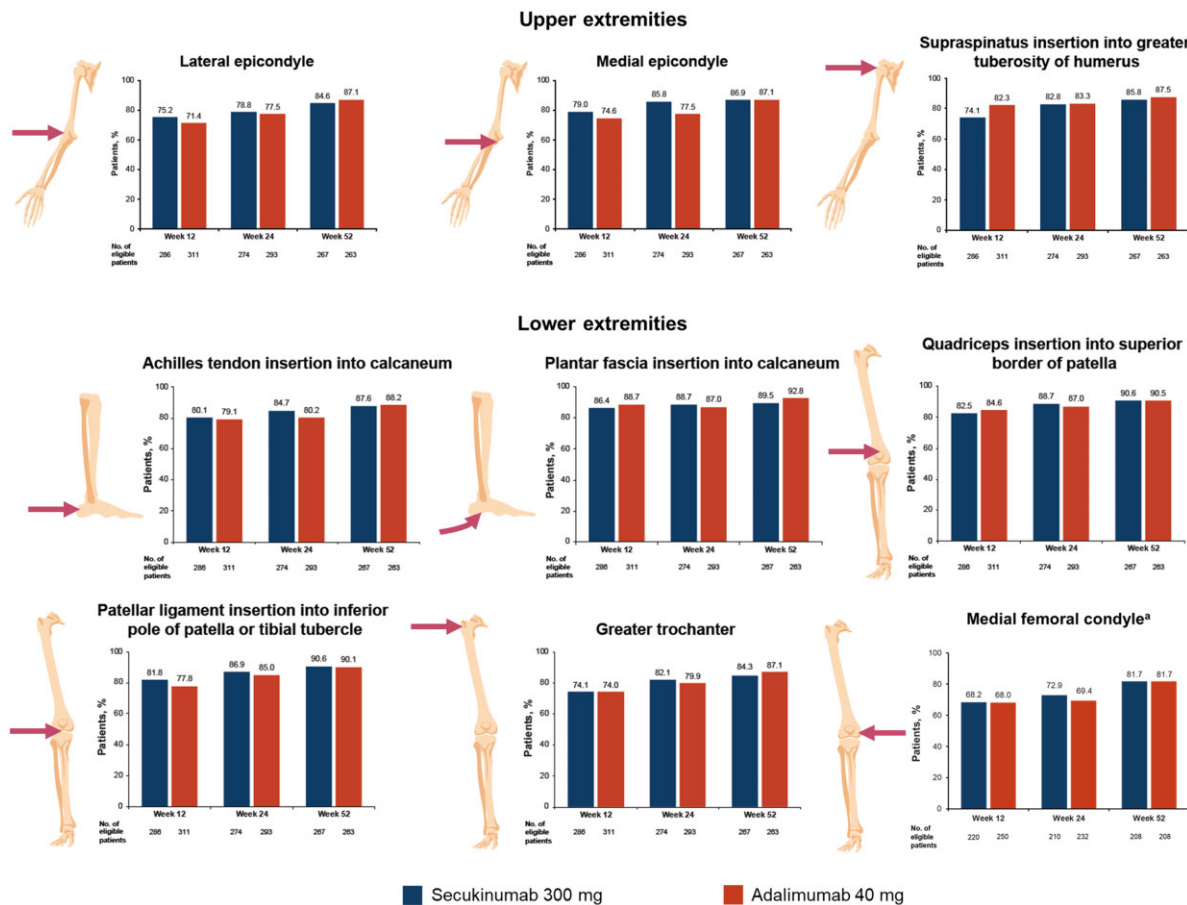


Figure 4. Patients achieving enthesitis resolution at SPARCC sites in the upper and lower extremities at weeks 12, 24, and 52. ^aMedial femoral condyle is measured by LEI and not SPARCC; results are presented for patients with enthesitis at baseline as measured by LEI. LEI: Leeds Enthesitis Index; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index

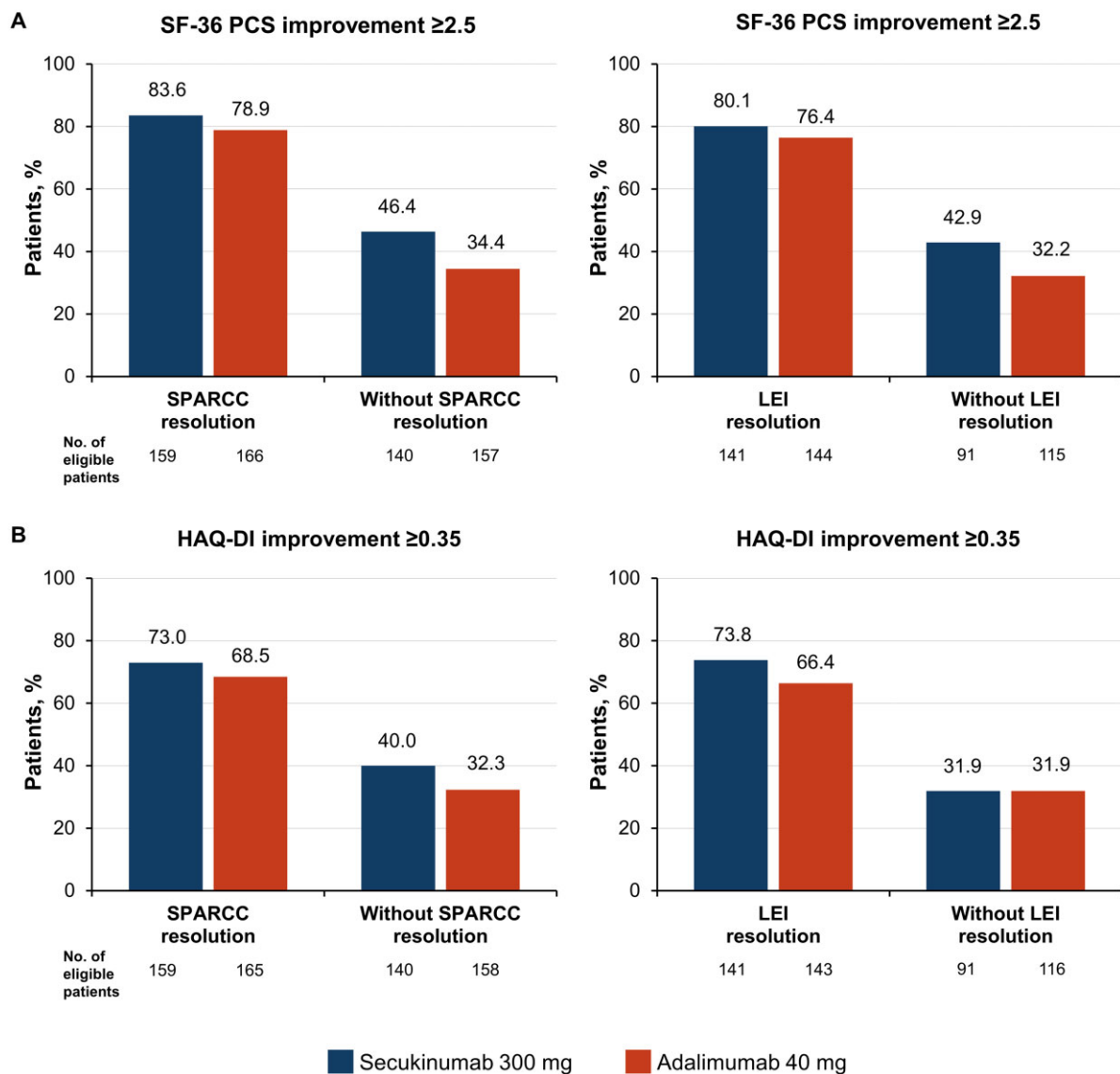


Figure 5. Achievement of (A) SF-36 PCS improvement ≥ 2.5 and (B) HAQ-DI improvement ≥ 0.35 by enthesitis status at week 52. HAQ-DI, HAQ-Disability Index; LEI: Leeds Enthesitis Index; PCS, physical component summary; SF-36, 36-Item Short Form Health Survey; SPARCC, Spondyloarthritis Research Consortium of Canada Enthesitis Index

imaging tools represent an excellent complement in the diagnosis and monitoring of enthesitis and other PsA signs [3, 25–27]. The lack of an imaging endpoint for enthesitis can be viewed as a limitation of the EXCEED study.

We observed that enthesitis relapse after initial resolution was infrequent for both the secukinumab and adalimumab groups. Additionally, most patients without enthesitis at baseline experienced no new enthesitis through 52 weeks of treatment with either drug, suggesting that inhibition of IL-17 or TNF signalling could provide some protection from enthesitis progression among patients with PsA.

The anatomical distribution of enthesitis at baseline was mostly balanced between the upper and lower extremities in both secukinumab and adalimumab groups in a pattern consistent with previous reports [28]. These analyses also highlight the early and sustained resolution of enthesitis through 52 weeks at site level with both drugs. Little difference was observed in treatment response among load-bearing joints of

the lower extremities compared with non-load-bearing joints of the upper extremities.

Improvements in PROs measuring HRQOL and disability seen with both drugs only partially reflect the consequence of improvement or resolution of enthesitis. Both the SF-36 PCS and HAQ-DI PROs indirectly capture impacts on enthesitis features and disease activity beyond those measured by LEI and SPARCC, such as axial enthesitis and other measures of PsA disease activity that consider the whole patient. For example, the EXCEED primary study demonstrated that patients receiving secukinumab experienced greater improvements in psoriasis *vs* those receiving adalimumab [14]. This difference in psoriasis response, for example, could partially underlie any small numerical improvements in PROs observed here among patients receiving secukinumab *vs* adalimumab.

bDMARDs are widely used in the treatment of PsA, although few studies have directly compared treatment response with different bDMARDs in a head-to-head manner.

The open-label, blinded-assessor SPIRIT-H2H study comparing the IL-17 inhibitor ixekizumab with adalimumab found significantly greater resolution of SPARCC enthesitis for patients receiving ixekizumab *vs* adalimumab at week 24 (56.6% *vs* 45.0%; $P=0.019$), although no significant differences in LEI resolution were observed at this time (59.7% *vs* 55.1%; $P=0.432$) [29]. Although a greater proportion of patients receiving ixekizumab had SPARCC enthesitis at baseline compared with those receiving adalimumab (67% *vs* 60%), mean (s.d.) baseline SPARCC scores were better for patients receiving ixekizumab than those receiving adalimumab (4.9 [3.5] *vs* 5.7 [3.8]) [29]. The enthesial sites assessed by SPARCC and LEI largely overlap; however, the sites are not identical, and the greater number of entheses assessed by SPARCC *vs* LEI could lead to increased sensitivity for detecting presence of enthesitis and response to treatment. By week 52 of SPIRIT-H2H, no differences in enthesitis resolution were observed with either drug as measured by LEI or SPARCC [30]. However, the open-label design of this study limits the interpretation of these results.

In the ECLIPSA study comparing the IL-12/23 inhibitor ustekinumab with adalimumab in patients with PsA and enthesitis, 73.9% of patients receiving ustekinumab achieved the primary endpoint of SPARCC resolution at week 24 compared with 41.7% of those receiving adalimumab ($P=0.007$) [31]. Interpretation of these results is limited by both the open-label study design and by the small study size (47 total enrolled patients).

In conclusion, this post hoc analysis of EXCEED is the first blinded, head-to-head study investigating detailed enthesitis response between two bDMARDs. Overall, the findings from this study indicate that secukinumab and adalimumab improve enthesitis among patients with PsA to a similar extent in terms of achievement of enthesitis resolution, timing of response, site-specific responses and occurrence of relapse after first resolution. Our findings suggest that inhibition of IL-17A with secukinumab can result in improvements over 52 weeks in enthesitis responses comparable to those achieved with adalimumab among patients with PsA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article are available in the article and in its online [supplementary material](#).

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