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Regression of peripheral subclinical enthesopathy in therapy-naïve patients treated with Ustekinumab for moderate-to-severe chronic plaque psoriasis

A 52-week, prospective, open label, feasibility study

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Running title – The effect of ustekinumab on subclinical enthesopathy psoriasis pateints

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ABSTRACT

Objective

This study investigated whether sonographically determined subclinical enthesopathy in patients with moderate-to-severe psoriasis regressed under therapy with ustekinumab, initiated for skin disease.

Methods

Seventy-three systemic therapy-naïve patients with moderate-to-severe psoriasis and without symptoms of PsA, and 23 healthy volunteers, were screened using ultrasound for subclinical enthesitis. Subsequently, 23 psoriasis patients with "inflammatory changes" on ultrasound were treated with ustekinumab for 52 weeks. The evolution of sonographic abnormalities was assessed using an extensive grey scale (GS) and power Doppler (PD) ultrasound protocol of the upper and lower limb entheses at weeks 0, 12, 24 and 52. For each parameter, a GS or PD score >0 was taken as abnormal and a summative score (based on the GUESS) calculated.

Results

49.3% of screened patients with psoriasis had at least one inflammatory entheseal abnormality on ultrasound. Mean inflammation scores were higher in psoriasis patients compared with healthy volunteers: 9.9 (6.6) vs. 1.0 (1.4). With treatment, mean (95% C.I.) inflammation scores reduced significantly from week 0 by 42.2% to week 24 (-4.2 (-6.3,-2.1), $p<0.001$) and by 47.5% (-4.7 (-7.1,-2.3), $p=0.001$) to week 52. Entheseal structural abnormalities did not significantly change during treatment.

Conclusion

IL-12/23 inhibition for psoriasis appears to suppress subclinical enthesopathy within 12 weeks of treatment, maintained to week 52. Further longitudinal studies are needed to see whether therapy initiated for skin disease may prevent PsA development.

Keywords

Subclinical enthesitis; psoriasis; psoriatic arthritis; ustekinumab; IL-23.

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INTRODUCTION

The recognition that psoriatic arthritis (PsA) can quickly lead to irreversible joint damage, functional limitation and quality-of-life impairment has prompted a shift in disease management towards earlier diagnosis and treatment (1). Given that 70% of patients who develop PsA have antecedent psoriasis, dermatologists are ideally positioned to identify joint abnormalities at the earliest juncture. In some psoriasis populations, around 2% of cases develop PsA each year (1). However, despite increasing dermatologist awareness and the promotion of screening for PsA in psoriasis patients, the prevalence of undiagnosed musculoskeletal disease remains high with undiagnosed PsA reported in up to 29% of patients attending the dermatology clinic (2).

Enthesitis is hypothesised to be the primary abnormality in PsA (3). Trials investigating the efficacy of biologic agents in PsA have shown improvements in clinical enthesitis as a secondary outcome measure (4). However, the presence of subclinical enthesopathy and associated osteitis has been reported in patients with psoriasis but no arthritis (5), for which clinical examination is ineffective. The sonographic response in subclinical enthesopathy to biologic drugs used in both psoriasis and established PsA is not well studied. One small observational study has reported a decrease in morphological sonographic abnormalities in psoriasis patients with enthesitis treated with methotrexate or TNF inhibition for six months, although a proportion of these patients fulfilled the CASPAR criteria for PsA (6).

Systemic IL-23 overexpression leads to a psoriatic-like spondyloarthropathy phenotype that commences at the enthesis (7). Given the clear role of IL-23 in the development of spondyloarthopathy-based, entheseal-driven pathology, a therapeutic strategy aimed at blocking the IL-23/17 axis would therefore pose a logical option for the treatment subclinical enthesopathy in early PsA. Therefore, we investigated the effect of IL-12/23 inhibition on the sonographic features of subclinical enthesopathy in patients with moderate to severe psoriasis, using skin-directed treatment with ustekinumab, a fully humanised monoclonal antibody directed against IL-12/IL23p40.

METHODS

Patients Groups

73 consecutive new adult patients with moderate-to-severe chronic plaque psoriasis (PASI>10) and no PsA (defined as the absence of clinically evident signs/symptoms of inflammatory arthritis to satisfy the CASPAR criteria and a PEST score of <3) and 23 healthy volunteers were scanned using ultrasound for subclinical enthesitis.

Exclusion criteria for both cohorts included any known rheumatological disease, a positive rheumatoid factor or anti-citrullinated protein antibody, and prior treatment with any DMARD for any condition. Only prior anti-psoriatic therapy with emollients, topical medicaments and narrowband ultraviolet phototherapy were permitted on the basis that prior systemic therapies may affect subclinical enthesopathy. Psoriasis patients were eligible for inclusion if they exhibited inflammatory sonographic changes that fulfilled the OMERACT

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definition of enthesopathy in at least one peripheral enthesis (8). Eligible patients with contraindication to receive ustekinumab were excluded.

Ultrasonography

Grey scale (GS) ultrasound and power Doppler (PD) examinations were performed by two dedicated research sonographers (LH and a second MSK sonographer) fully trained in entheseal ultrasound using a Logiq E9 machine (General Electric®, Wauwatosa, Wisconsin USA). The sonographers were aware of the patients' diagnosis of psoriasis. It was not possible to blind the sonographers to the study visits due to the same sonographers performing the scans and the small number of participants in the trial.

Patients with psoriasis underwent an initial ultrasound of the upper and lower limb entheses and adjacent bursae to screen for the presence of subclinical inflammation, and were eligible if they exhibited thickening, hypoechoic change and/or PD signal in at least one enthesis. Examined entheseal sites are listed in Table 1S.

Ultrasonography was performed in eligible patients at baseline (day of first dose) and after 12, 24 and 52 weeks of therapy. The sites examined were identical to the screening ultrasound, but with the exemption of the third, fourth and fifth digits of the hands as they were found to yield little or no enthesitis at screening. Healthy volunteers had one ultrasound.

Entheses of the flexor and extensor pollicus longus, flexor digitorum profundus, extensor digitorum, common extensor and flexor, distal brachial triceps, quadriceps, proximal and distal patellar, Achilles, plantar aponeurosis and peroneal brevis tendons were assessed.

Ultrasound Image Interpretation

The OMERACT definition of enthesopathy was used to interpret ultrasound images. Each entheseal site was assessed for: thickening, hypoechogeneity, PD signal and calcification, and adjacent enthesophytes, bone erosions and cortex irregularities. Cortex irregularity and bursal involvement were included since cortex irregularity may reflect cumulative damage from previous bouts of inflammation and since bursal involvement indicates synovio-entheseal complex involvement- a key lesion that might be involved in the transition from subclinical enthesopathy to PsA. GS and PD bursal hypertrophy were also assessed at perientheseal sites (Table 1S).

Entheseal thickening was assessed at the widest point of the entheseal insertion on longitudinal scans. A previously published quantitative scoring system was applied to the measurements and normal values were accepted as reported in the literature where available. Where unavailable, the method employed by Gibbon and Long was employed (9), which informed the published plantar fascia threshold used in the Glasgow Ultrasound Enthesitis Scoring System (GUESS) (10). The upper limit of tendon thickness in our healthy volunteer cohort was used as the threshold for patients with psoriasis.

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Drug Therapy

Ustekinumab was provided at the licensed dose subcutaneously (weight <100kg: 45mg; ≥100kg: 90mg) at weeks 0, 4, 16, 28, 40 and 52 and administered by the clinician to ensure compliance. Some concomitant topical psoriasis therapies were permitted (emollients, topical corticosteroids, coal tar preparations and vitamin D analogues). Corticosteroids, regular NSAIDs, systemic immunosuppressants or any experimental drug(s) were prohibited.

Clinical Assessment

Clinical assessments were performed prior to each ultrasound by a dermatologist (LS) trained in musculoskeletal examination with an additional safety visit at week 4. Assessments included the PASI score, percentage body surface area (BSA), mNAPSI score, documentation of anatomical sites with psoriasis and assessments for enthesitis (30 sites), dactylitis and peripheral joint swelling and/or tenderness (66/68 joints).

Statistical Analysis

This study was designed as a pilot to inform a larger randomised control trial. The sample size for the treatment phase was based on published "rules of thumb" suggesting between 12 and 30 patients should be recruited to pilot studies. We aimed to recruit at least 12, up to 30, depending on the recruitment rate, which was a feasibility outcome of the trial.

RESULTS

Participant Characteristics

73 patients (45 male, 23 female) with moderate-to-severe plaque psoriasis (median [IQR] PASI 17.6 [11.9, 25.4]) underwent a screening ultrasound. 36 (49.3%) had ≥1 sonographic inflammatory abnormality fulfilling the OMERACT definition of enthesopathy. 30 of these 36 patients met trial eligibility criteria, of which six chose conventional therapy and one was lost to follow up. 23 patients consented to trial participation and were treated with ustekinumab (Figure 1S). Attempts were made to recruit volunteers with similar characteristics (age, sex, BMI) to the patient group, although specific case matching was not performed (Table 1). No clinically meaningful differences in age [mean (95% CI) 4.8 (-2.0, 11.6) years] and BMI [median difference (95% CI) 3.3 (0.1, 6.7) kg/m^2] were found.

Pre-treatment ultrasonographic abnormalities in patients with psoriasis compared with healthy volunteers

Entheseal Inflammation

24.2% of 598 entheses scanned in psoriasis patients at week 0 (median (IQR) 6 (4,9) out of 26 per patient) had at least one inflammatory entheseal abnormality (thickening, hypoechogeneity and/or PD signal) with a score >0 compared to 4.5% of 598 entheses in

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volunteers (median (IQR) 1 (0,1) out of 26 per volunteer). In total, 187 inflammatory abnormalities were seen in patients with psoriasis (mean (± s.d.) 8.7 (4.7) abnormalities per patient), compared with 24 in healthy volunteers (1.0 (1.4) abnormalities per volunteer). Mean (s.d.) inflammation scores were higher in patients with psoriasis at 9.9 (6.6) out of a possible 294 compared with 1.0 (1.4) in the healthy volunteer group. In both groups, abnormalities were seen with greatest frequency in the knee tendons (distal patellar > quadriceps), followed by the common extensor and flexor tendons of the elbow and large entheses of the ankle (Table 4S). Bursitis was minimal; one patient had GS hypertrophy in one superficial infrapatellar bursa and the contralateral deep infrapatellar bursa, and one volunteer in one retrocalcaneal bursa at week 0. At the clinical assessment, an overall, 29 tender enthesis sites were identified from 736 examined in all 23 patients (3.9%) and 4 patients had asymptomatic toe swelling consistent with low grade dactylitis.

Entheseal Chronic Damage

15.9% of 598 entheses at week 0 (median (IQR) 5 (2,8) out of 26 per patient) had at least one chronic abnormality indicative of structural damage with a score >0 compared to 6.0% of 598 in volunteers (1 (0,3) per participant). In total, 137 abnormalities were identified in the psoriasis group (mean (s.d.) 6.0 (4.7) abnormalities per patient), compared with 36 in healthy volunteers (1.6 (1.6) abnormalities per volunteer). Mean (s.d.) chronicity scores were higher in patients with psoriasis at 7.9 (5.7) out of a possible total of 312, compared with 2.0 (1.9) in the healthy volunteer group.

Cutaneous responses to ustekinumab in participants with psoriasis

Median (IQR) duration of psoriasis was 11 (7-25) years. Median baseline PASI and BSA were 18.0 and 30%, respectively. 21 patients (91.3%) achieved a PASI 75 response, 17 patients (73.9%) achieved a PASI 90 response and 11 patients (47.8%) achieved a PASI 100 response by the primary endpoint of week 24 (Table 3S) and responses were generally maintained out to week 52. 17 patients had nail involvement at baseline (median mNAPSI 28/140). Median mNAPSI scores decreased significantly, by 15 points and 22 points at weeks 24 and 52 respectively.

Ultrasonographic musculoskeletal responses to ustekinumab in patients with psoriasis

Entheseal Inflammation

Mean entheseal inflammation scores reduced from week 0 by 42.2% to week 24 (mean (95% C.I.) reduction -4.2(-6.3,-2.1) d=1.2, p<0.001) and by 47.5% (-4.7 (-7.1,-2.3) d=1.3, p=0.001) to week 52 (Figure 1). The percentage of entheses with at least one inflammatory abnormality decreased from 24.2% to 14.0% by week 24, and to 10.4% by week 52. Of the 187 inflammatory abnormalities found at baseline, 116 (62.0%) resolved, 4 (7.5%) improved, 55 (29.4%) remained unchanged and two (1.1%) worsened by week 24. An example of

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resolution of subclinical enthesopathy is shown in Figure 2. 38 new abnormalities developed on treatment by the primary endpoint of week 24 (Table 7S). The mean (s.d.) total number of abnormalities per patient decreased from 8.1 (4.7) at week 0 to 5.7 (3.8) lesions (difference (95% C.I.) -2.5 (-3.6,-1.3)) at week 12, to 4.7 (4.2) lesions (difference -3.4 (-4.9,-1.9)) at week 24 and to 3.5 (2.7) lesions (difference -4.7 (-6.6, -2.7)) at week 52. Bursitis resolved in the patient with two affected areas at baseline by week 24. Three patients developed transient unilateral bursal synovial hypertrophy in one area during the study, with resolution at the following scan in all cases. No substantive differences were seen in inflammatory enthesopathy scores based on age, gender, BMI, smoking status, alcohol consumption, duration of psoriasis, anatomical location of psoriatic plaques, family history or HLA-Cw06 status at any time point.

Entheseal Chronic Damage

Structural abnormalities remained static or marginally worsened over time. Mean entheseal chronic damage scores increased by 16.5% between week 0 and week 24 (mean (95% C.I. increase 1.3 (-0.2,2.7) d=0.5, p<0.082), and by 10% (0.8 (-1.6,3.1) d=0.2, p=0.512) between week 0 and week 52 (Figure 1). The percentage of entheses with at least one chronic damage abnormality increased from 15.9% at week 0 to 18.6% at week 24 and 20.0% at week 52. Of the 137 chronic damage abnormalities found at week 0, 35 (25.5%) resolved, 14 (10.2%) improved, 75 (54.7%) remained unchanged and 13 (9.5%) worsened by week 24. 68 new abnormalities developed on treatment. Mean (s.d.) total number of abnormalities per patient changed from 6.0 (4.7) at week 0 to 5.6 (5.0), 7.4 (5.7) and 7.6 (6.1) at weeks 12, 24 and 52 respectively.

DISCUSSION

Our findings confirm that subclinical enthesopathy in patients with psoriasis is not uncommon, with 49.3% of the 73 patients with moderate to severe psoriasis having at least one potentially modifiable inflammatory abnormality at first presentation to dermatology. This is in broad agreement with recent MRI findings in psoriasis but higher than that reported on previous more limited ultrasound protocols (11, 12). We have shown that targeted treatment of psoriasis with a therapeutic agent that independently has been shown to work in PsA, namely anti-IL12/23p40, can be associated with regression of subclinical inflammatory entheseal and synovial abnormalities. However, US determined chronic damage abnormalities did not significantly progress. Our findings support the concept that therapies that suppress subclinical enthesopathy may have the potential to prevent arthritis development, at least in a subset of cases, but this needs formal testing in longitudinal studies.

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To evaluate the effect of therapy on subclinical skeletal abnormalities in psoriasis, we used a more comprehensive ultrasound scoring system based on the GUESS score. GUESS was chosen as it is an easily reproducible, standardised measure of sonographic lower limb entheseal abnormalities. However, it excludes several accessible entheses that have not been reliably investigated in patients with subclinical disease (notably those in the upper limbs), and also excludes parameters such as hypoechogeneity, PD signal and bone cortex irregularities that are a fundamental part of the OMERACT consensus definition of enthesopathy. Whilst important to include, PD signal was a rare finding, with only 0.2% of entheses exhibiting signal in patients with psoriasis prior to treatment. This is less than the 1-7.4% previously reported in other psoriasis cohorts (5, 12), which may be due to a dilutional effect from the inclusion of many more entheseal sites and the investigation of asymptomatic patients. In keeping with previous studies, patients in this study exhibited the most abnormalities in the larger entheses, such as the quadriceps, proximal and distal patella, common extensor and Achilles tendon insertions. However, reflecting the heterogeneous nature of PsA, abnormalities in the smaller entheses were not infrequent (10-20%), especially in the extensor and flexor pollicis longus tendon insertions of the thumb, the peroneal brevis enthesis and flexor digitorum profundus enthesis of the index finger.

Chronic damage abnormalities did not change markedly in our cohort with ustekinumab therapy. While some structural lesions worsened, some appeared to decrease in severity or resolve, principally bone erosions, which is a recognised phenomenon in RA (13) and has also been shown in PsA (14). Rates of progression of structural lesions without therapy are not known; inclusion of an untreated group may have helped determine if ustekinumab slowed the development of damage. However, this limitation is hard to overcome, as it would be unethical to not treat a group of patients presenting for treatment of psoriasis. In this study, we attempted to recruit control patients with psoriasis undergoing narrowband UVB phototherapy for comparison but this proved unfeasible. Similarly, it may have been helpful to re-scan the healthy volunteers after 24 weeks to indicate the rates of progression the normal population. High rates of structural damage were seen at the Achilles tendon enthesis in our healthy volunteer cohort (30.4% compared to 17.4% in patients), but the inverse was seen in inflammatory abnormalities (4.3% in volunteers, 15.2% in patients), suggesting that in volunteers, the structural changes were due to trauma and natural degeneration rather than an inflammatory process.

To the best of our knowledge, this is the first study to evaluate the alteration in sonographic features of subclinical enthesitis with an IL-12/IL-23p40 inhibitor and the first to investigate sonographic treatment responses in asymptomatic psoriasis patients who are systemic therapy naive. However, another recent study reported in abstract form has also shown that downstream inhibition of IL-17 may have a similar effect on subclinical PsA (15).

The relatively small number of patients investigated in the current pilot study prevents any definite conclusions from being drawn on the effectiveness of ustekinumab in treating subclinical enthesitis and bursitis, although the trends identified are encouraging. Since this

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was an open label study there is a possibility of bias in the longitudinal imaging assessment of cases even though the imaging was performed in a dark room, with limited verbal interaction with the cases and where other patients in different studies were having sonographic assessment.

These data are in keeping with recently published reports of good sonographic responses in entheseal abnormalities after treatment with TNF inhibitors in patients with psoriasis (6) and spondyloarthritis (16). Overall, the results of our proof-of-concept study support the role of IL-12/23 in entheseal-driven pathology in the earliest stages of PsA and promote the need for larger trials to ascertain whether the regression of subclinical arthropathy is indeed associated with PsA prevention.

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COMPETING INTERESTS

None

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Tables

Table 1. Descriptive characteristics of the two study populations (IQR: Interquartile range)

Characteristic		**Psoriasis Patients**	**Healthy Volunteers**
N		23	23
Gender, *n (%)*	Male	12 (52.2%)	12 (52.2%)
	Female	11 (47.8%)	11 (47.8%)
Age (years), *mean (SD; range)*		44.1 (13.9; 20-74)	39.3 (8.3; 22-59)
Skin Type, *n (%)*	I	3 (13.0%)	4 (17.4%)
	II	11 (47.8%)	14 (60.9%)
	III	8 (34.8%)	4 (17.4%)
	IV	0 (0%)	1 (4.3%)
	V	1 (4.3%)	0 (0%)
	VI	0 (0%)	0 (0%)
BMI (kg/m^2), *median (IQR)*		29.6 (27.6, 29.6)	26.8 (24.6, 31.5)
Smoking Status, *n (%)*	Never	8 (34.8%)	18 (78.3%)
	Current	7 (30.4%)	1 (4.3%)
	Previous	8 (34.8%)	4 (17.4%)
	Ever	15 (65.2%)	5 (21.7%)
Cigarette pack years in current/ex smokers (years), *median (IQR)*		20 (7, 32)	7.9 (4, 12)
Alcohol consumption in drinkers (units/week), *median (IQR)*		10 (10, 20)	10 (10, 20)
Positive family history of psoriasis, *n (%)*		13 (56.5%)	2 (8.7%)
Positive family history of psoriatic arthritis, *n (%)*		2 (8.7%)	0 (0%)
Positive family history of other rheumatological disorder, *n (%)*		4 (17.4%)	10 (43.5%)
Positive family history of autoimmune disease, *n (%)*		2 (8.7%)	6 (26.1%)

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Legends for figures

Figure 1. Change over time in total enthesopathy scores for inflammatory and chronic damage abnormalities in patients treated with ustekinumab. Progressive improvement of lesions deemed to be potentially inflammatory was evident (red) but chronic changes showed to significant difference (blue).

Figure 2. Ultrasound image showing resolution of subclinical enthesopathy. Reduction in entheseal thickness (†, grade 2 to 0), hypoechogenicity (✶, grade 1 to 0) and power doppler signal (▲, grade 3 to 0) within the left proximal patellar tendon enthesis between week 0 (a) and week 52 of ustekinumab therapy (b). PT: Patellar tendon; Pat: Patella; Tib: Tibia.

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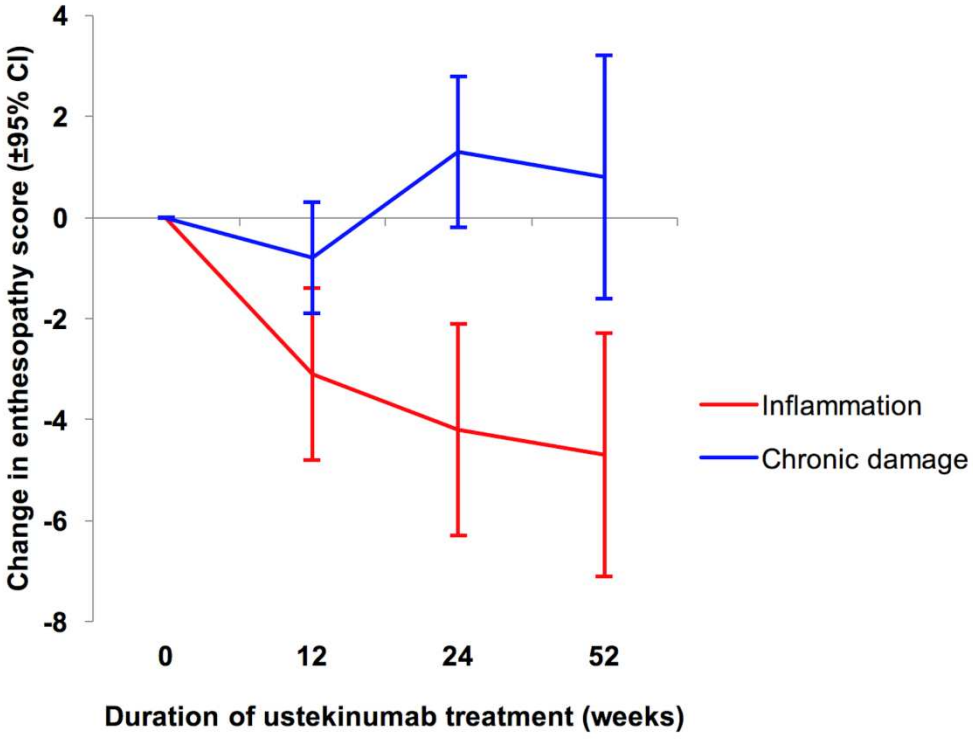

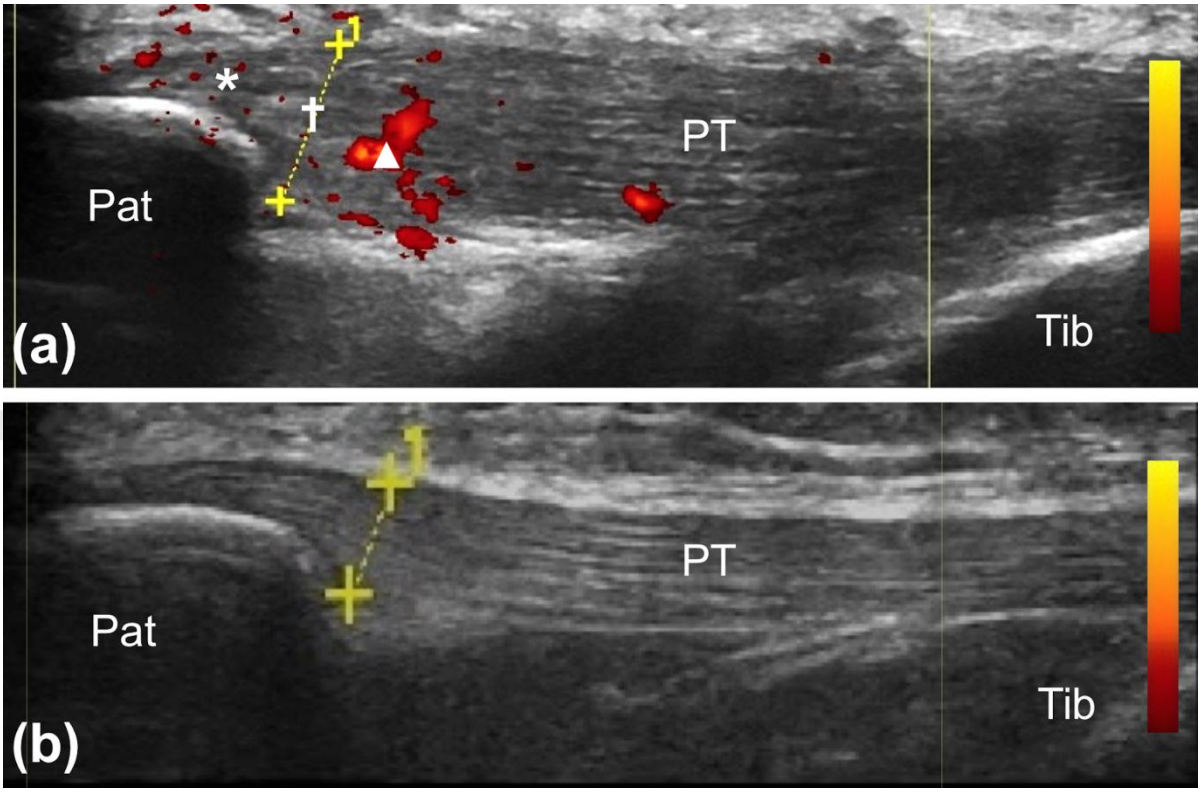

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