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Original article

Usefulness of ultrasound in the assessment of the efficacy of apremilast in psoriatic arthritis: Articular, enthesitic and nail index

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ABSTRACT

Background: Psoriatic arthritis (PsA) affects joints and entheses. The objective is to use ultrasound (US) to see inflammatory changes in joints and entheses in patients with active PsA starting Apremilast. Primary objective: 20% reduction in the US index (UIC) at 12 months.
Methodology: Multicenter, prospective, open-label study. Patients with PsA (≥2 swollen joints) and ≥2 US synovitis in joints and ≥1 US enthesitis at screening were recruited. Follow-up was 52 weeks (baseline and 1, 6, 9, 12 months). US (joint, tendon, and entheses), clinical (SJC, TJC, LEI, PGA, PtGA), and biological (ESR and CRP) parameters were recorded.
Results: 48 patients were evaluated, 46 were included in the follow-up and 26 completed the 52-week study. The primary endpoint was achieved, with reductions of up to 40%. All clinical and ultrasound variables decreased significantly after 12 months. 75 adverse events (AEs) were recorded in 33 patients, and only one serious event (SAE). Reasons for withdrawal included AEs (6 patients), lack of efficacy (8 patients), and other reasons (loss to follow-up, withdrawal of consent) for 6 patients.
Conclusions: Changes in different domains of PsA in patients treated with Apremilast can be best identified by ultrasound. Ultrasound is an excellent tool to study joints, tendons, and entheses in PsA. Apremilast is a safe, well-tolerated, and effective treatment for several patterns of PsA (joints, entheses) as demonstrated by ultrasound. Ultrasound can also identify nail diseases in patients with PsA.

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Utilidad de la ecografía en la evaluación de la eficacia del apremilast en la artritis psoriásica. Índice articular, entésico y ungueal

Palabras clave:
Artritis psoriásica
Ultrasonido
Apremilast

R E S U M E N

Antecedentes: La artritis psoriásica (APs) afecta a articulaciones y entesis. El objetivo es utilizar la ecografía (US) para ver los cambios inflamatorios en articulaciones y entesis en pacientes con APs activa que inician tratamiento con apremilast. Objetivo primario: reducción del 20% en el índice US (UIC) a los 12 meses.
Metodología: Estudio multicéntrico, prospectivo, abierto. Se reclutaron pacientes con APs ($\geq$ 2 articulaciones inflamadas) y $\geq$ 2 sinovitis US en articulaciones y $\geq$ 1 entesitis US en el momento de la selección. El seguimiento fue de 52 semanas (basal y 1, 6, 9 y 12 meses). Se registraron parámetros US (articulares, tendones y entesis), clínicos (SJC, TJC, LEI, PGA y PtGA) y biológicos (ESR y CRP).
Resultados: Se evaluaron 48 pacientes, 46 fueron incluidos en el seguimiento y 26 completaron el estudio de 52 semanas. Se logró el objetivo primario, con reducciones de hasta el 40%. Todas las variables clínicas y ecográficas disminuyeron significativamente después de 12 meses. Se registraron 75 eventos adversos (EA) en 33 pacientes, y solo un evento grave (EAG). Las razones de retiro incluyeron EA (6 pacientes), falta de eficacia (8 pacientes) y otras razones (pérdida de seguimiento, retiro del consentimiento) para 6 pacientes.
Conclusiones: Los cambios en diferentes dominios de la APs en los pacientes tratados con apremilast se pueden identificar mejor mediante ecografía. La ecografía es una excelente herramienta para estudiar articulaciones, tendones y entesis en la APs. Apremilast es un tratamiento seguro, bien tolerado y eficaz para varios patrones de APs (articulaciones, entesis) como se demuestra mediante ecografía. La ecografía también puede identificar onicopatía en los pacientes con APs.

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease. Clinical manifestations are very heterogeneous, ranging from mono/oligoarticular/polyarticular, periarticular (tendon, enthesis, dactylitis) and axial involvement. In the peripheral forms, several methods are used to evaluate the disease and the therapeutic response.[1] Clinical index created for this disease, as Disease Activity in Psoriatic Arthritis (DAPSA), and others like Disease Activity Score index on 28 joints (DAS28), MASES (a clinical index for enthesitis) not fully evaluate the spectrum of manifestations and localizations of the disease. In addition, sometimes they underestimate the degree and/or intensity of the inflammation that occurs in the PsA.

Hence, we need better tools for a more objective assessment of the inflammatory process presented by each patient. Therefore, imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are increasingly being used in the evaluation of this disease.[2,3]

Ultrasound has demonstrated its usefulness in the diagnosis and monitoring of inflammatory and chronic lesions in PsA patients.[4–8] However, no studies have shown ultrasound joint and enthesis changes in PsA patients after the initiation of a therapy.

The use of joint ultrasound has already demonstrated to be a good tool for both joint (68 joints) and periarticular assessment (14 entheses) in patients with PsA.[9] Furthermore, imaging techniques have also been used for the evaluation of skin domains such as skin and nail. Previous works have suggested a close connection between subungueal enthesitis and the development of PsA.[10] Recently, a new simplified ultrasound index, more feasible in clinical practice than the previous ones, have shown good reproducibility for the monitoring of joint and periarticular activity.[11] This index, called PsASon22 and PsASon13 (according to the number of areas assessed) has shown to be sensitive to change, valid and reproducible.

Apremilast, a phosphodiesterase4 (PDE4) inhibitor. PDE4 is the major enzyme class responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), an intracellular second messenger that controls a network of pro-inflammatory and anti-inflammatory mediators. Apremilast is an orally available targeted PDE4 inhibitor that modulates a wide array of inflammatory mediators involved in psoriasis and psoriatic arthritis, including decreases in the expression of inducible nitric oxide synthase, TNF-α, and interleukin (IL)-23 and increases IL-10. This drug has been shown to be effective in many of the clinical manifestations of PsA.[12–15]

This study aims to assess ultrasound changes in joints and entheses of patients with active PsA who started treatment with Apremilast after failure or intolerance to conventional synthetic Disease Modifying Anti Rheumatic Drugs (csDMARD)

Methods

A phase IV, multicenter, prospective and open-label clinical trial conducted in 9 centers in Barcelona, Spain, from March 2018 until June 2021.

The study was approved by the ethical committee (PSA-PI-006421, EudraCT (No.) 2017-000901-19).

We hypothesize that ultrasound will objectively demonstrate the efficacy of Apremilast in the treatment of patients with active PsA. The primary objective was a 20% reduction in the ultrasound index 12 months after the introduction of Apremilast. Secondary objectives were: 50% and 70% reduction in the ultrasound index at 12 months (similar to the ACR objectives in treatment efficacy evaluation), assessment and characterization of the nail-associated ultrasound lesions in PsA (diffuse thickening or patching of the nail ventral lamina, detection of nail changes in relation to treatment with Apremilast, reduction of thickness of the nail bed with respect to the baseline mean value, correlation of nail and ultrasound/articular ultrasound index changes), correlation of the ultrasound variables with changes in the number of swollen and tender joints, changes in Patient VAS (0–100 mm) or PtGA, physician VAS (0–100 mm) or PGA, changes in the LEI index, and changes in CRP and ESR.

Patients

The study was conducted in accordance with the protocol, the Good Clinical Practice (GCP) guidelines, and the ethical principles of the latest revision of the Declaration of Helsinki adopted by

the World Medical Association. Patients attending the trial centers underwent routine assessments, and if meeting eligibility criteria they were included in the study. All of them received 30 mg Apremilast administered twice daily for 52 weeks.

Inclusion criteria: Adults 18 years or older with Psoriatic Arthritis (PsA) according to CASPAR (Classification Criteria for Psoriatic Arthritis) criteria at the time of selection. Active clinical disease (more than two swollen joints). Ultrasound synovitis in ≥2 joints and ≥1 enthesitis at the screening visit. Accept and sign the informed consent of the study. Ability to comply with all tests and visits of specified protocol and have a permanent address. Women of childbearing potential must have a negative pregnancy test at the baseline visit. Women of childbearing potential who participate in the study should use contraceptive methods throughout the trial and for at least 28 days after taking the last dose of study medication.

Exclusion criteria: Concomitant treatment with methotrexate, leflunomide, or other DMARDs. Patients were not permitted to receive MTX during the month prior to screening. Prior or current use of biological therapy (anti-TNF). Failure to meet any of the inclusion requirements. Medical contraindications for taking Apremilast. Pregnancy or breastfeeding. History of allergy to any component of the study drug. Active tuberculosis (TB) or history of incomplete treatment for tuberculosis. Substance abuse or history of substance abuse within 6 months prior to screening. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks prior to screening; malignancy or history of malignancy (except in situ basal or squamous cell skin carcinomas treated [i.e. cured] and treated cervical intraepithelial neoplasms [i.e. cured] or carcinoma in situ of the cervix without evidence of recurrence within the last 5 years); use of systemic corticosteroids at doses >10 mg/day at the time of screening and 4 weeks before; use of potent cytochrome CYP3A4 enzyme inducers (e.g., rifampicin, phenobarbital, carbamazepine, phenytoin, St. John's wort and grapefruit juice) at the time of screening 4 weeks before or during the study; use of phototherapy within 4 weeks prior to screening (i.e., Ultraviolet B (UVB), psoralen and ultraviolet A (PUVA); use of any investigational drug within 4 weeks prior to screening; prior treatment with Apremilast.

Study medication may also be withdrawn from subjects who correspond to any of the cases listed below: whenever patients decide to do so, appearance of an adverse event that in the opinion of the investigator warrants the interruption of treatment, if there are significant violations of the protocol or for other duly justified reasons, if based on clinical criteria the patient could benefit from another treatment.

Visits

The study had 6 visits, Screening visit (day −7), Baseline visit (day −7 to day 0. Window +/− 2 days. May coincide with screening visit), 1 month visit (window of +/− 3 days), 6-month visit (window of +/− 7 days), 9-month visit (window of +/− 7 days) and 12-month visit (window of +/− 15 days).

Clinical

For clinical monitoring, the following variables were collected weight (kg), size (cm) (only at baseline), number of tender and swollen joints (TJC and SJC), patient VAS (0–100 mm) or PtGA, physician VAS (0–100 mm) or PGA, and Leeds Enthesitis Index (LEI).

Clinical remission was considered when the sum of clinical variables were less than 5 (PGA, PtGA, LEI, TJC, SJC).

Hematological and biochemical analysis were performed for biological monitorization in each visit.

Ultrasound

The ultrasound exams were done by a single rheumatologist expert in musculoskeletal ultrasound in each center. Ultrasonographer was blinded to the other parts of the study and previous visits. All the exams were done the same day as clinical evaluation, following EULAR recommendations for ultrasound study[16] examinations. Before the study was conducting a meeting to standardize ultrasound procedures and did a reliability test.

The ultrasound evaluation was conducted as follows: Joint assessment (JUS) included grayscale and power Doppler examinations of joints and tendons in the following anatomical regions: wrist, bilateral metacarpophalangeal joints of the 2nd, 3rd, and 5th fingers, bilateral proximal interphalangeal joints (PIP) of the 2nd and 3rd fingers, bilateral distal interphalangeal joints (DIP) of the 2nd and 3rd fingers, knees, bilateral first metatarsophalangeal joints (MTP), and third interphalangeal joints (IFD) of both feet. Enthesis assessment (EUS) involved grayscale and power Doppler evaluations at locations defined in the LEI index, including the tricipital, distal patellar, and Achilles enthesis. In each enthesis the following elemental lesions were evaluated: echogenicity, thickness, erosions, calcifications/enthesophytes, Doppler at enthesis, and bursitis (synovitis and Doppler).

In the study, a total of 11 joints bilaterally were evaluated using a semiquantitative scale from 0 to 3 for both grayscale and Power Doppler. This gives a maximum score of 132 (66 right and 66 left). Regarding the entheses, we evaluated 3 bilaterally, also using a semiquantitative scale from 0 to 3 in grayscale (normal, mild, moderate with some minor erosion and/or small calcification, and severe with big erosions and/or great enthesophytes) and 0 to 3 in Power Doppler (normal, isolated vessels, confluent vessels in less than 50% in 2 mm enthesis, and confluent vessels in more than 50% in 2 mm enthesis). This gives a maximum score of 36. The total range (JEUS) was from 0 to 168. This value was utilized in each ultrasound assessment to evaluate treatment effectiveness or response (primary objective). Comparisons were made between values obtained at each visit and the baseline.

For nail evaluation before and after treatment, the nails of the same fingers included in the joint assessment were examined at all time points. The aim of this sub-study was to demonstrate the relationship between nail changes and joint/enthesis changes, and whether they were associated with joint/enthesis lesions simultaneously. Ultrasound evaluation of each nail region included assessment of diffuse thickening or patching of the nail ventral plate, and measurement of nail bed thickness (mm).

Statistical methods

The study included a minimum sample size of 45 patients A reduction from 15% to 25% (effect size 0.5) in the ultrasound index 12 months after the introduction of Apremilast was expected, with an effect measure of 0.5, a type I error of 5%, and a power of 95%. As only 25 completed 80%.

An analysis of the characteristics of the evaluated population was carried out, including the inclusion and exclusion criteria, the number of valid visits, incompleteness, and abandonment. A descriptive analysis of the baseline characteristics of the sample was performed, presenting frequencies and percentages for qualitative variables, and means (standard deviation), medians, and interquartile ranges for quantitative variables.

The primary variable response was evaluated in two ways:

The percentage change from baseline was calculated using the formula: UIC = Change in ultrasound index = ([Final Ultrasound Index − Basal Ultrasound Index]/Basal Ultrasound Index) × 100. Confidence intervals were calculated, and a one-sample *t*-test was

Table 1
The table illustrates the changes in clinical and ultrasound parameters over the study duration.

Predictors	LEI	TJC	SJC	PGA	PtGA	JUS	EUS	JEUS	*N*
Visit 0	1.4(1.6) [0.9;1.9] 1 [0, 2]	5.8(5.8) [4.1;7.6] 5 [2, 6]	3.2(2.4) [2.5;3.9] 3 [2, 4]	5.6(1.2) [5.2;6] 5.8 [5, 7]	6.2(1.9) [5.6;6.8] 6.9 [5, 7]	17.6(11) [14.3;20.9] 15 [9, 25]	6(3.9) [4.9;7.2] 5 [3, 9]	23.6(12.6) [19.9;27.4] 23 [14, 29]	46
Visit 1 (1 m)	−0.36 1(1.3) [0.7;1.4] 0 [0, 2] **0.058**	−1.42 4.4(4.8) [3;5.8] 3 [1, 6] **0.038**	−1.11 −2.1(2.2) [1.4;2.7] 2 [0, 3] **<0.001**	−1.50 4.1(2) [3.5;4.7] 4[2, 6] **<0.001**	−1.06 5.1(2.5) [4.4;5.9] 5 [3.8, 7] **<0.001**	−5.22 12.4(8.5) [9.8;15] 11 [7, 16] **<0.001**	−2.09 3.9(3.1) [3;4.9] 4 [2, 5] **<0.001**	−7.31 16.3(9.8) [13.4;19.3] 13 [10, 22] **<0.001**	46
Visit 2 (6 m)	−0.55 0.9(1.2) [0.5;1.4] 0 [0, 2] **0.002**	−3.31 2.9(4) [1.4;4.4] 1 [0, 4] **0.002**	−2.27 0.9(1.8) [0.3;1.6] 0 [0, 1] **<0.001**	−2.89 2.4(1.9) [1.8;3.1] 2 [1, 3.7] **<0.001**	−2.47 3.4(1.9) [2.7;4.1] 3 [2, 4.5] **<0.001**	−8.74 9.2(7.2) [6.5;11.8] 7 [4, 13] **<0.001**	−2.44 3.7(2.8) [2.7;4.7] 3 [1.5, 6] **<0.001**	−11.25 12.(8) [9.9;15.8] 12 [6.5, 18.5] **<0.001**	32
Visit 3 (9 m)	−0.86 0.5(1.1) [0.1;0.9] 0 [0, 0.5] **0.001**	−3.09 2.4(3.6) [1;3.8] 1 [0, 3] **<0.001**	−2.08 1.1(1.9) [0.4;1.9] 0 [0, 1.5 **<0.001**	−2.96 2.4(1.9) [1.7;3.2] 2 [1, 3.8] **<0.001**	−2.86 3.1(2.4) [2.1;4] 2.5[1.5, 4.8] **<0.001**	−10.16 7.9 (8.1) [4.7;11.1] 5 [2, 11.5] **<0.001**	−3.02 3.3(3) [2.1;4.5] 3 [1, 4.5] **<0.001**	−13.36 11.1(9.5) [7.4;14.9] 9 [4, 15.5] **<0.001**	29
Visit 4 (12 m)	−0.68 0.8(1.2) [0.3;1.3] 0 [0, 1.8] **0.010**	−2.64 3(4) [1.4;4.6] 1 [0, 5] **0.009**	−2.04 1(1.4) [0.5;1.6] 0 [0, 2] **<0.001**	−2.62 2.6(1.9) [1.8;3.4] 2.4 [1, 4] **<0.001**	−1.98 3.8(2.1) [3;4.7] 4 [2, 5.2] **<0.001**	−9.72 7.5(6.7) [4.9;10.2] 4.5 [2.2, 10] **<0.001**	−3.05 3.2(2.5) [2.2;4.2] 3 [1.2, 4] **<0.001**	−12.70 10.7(7.6) [7.7;13.8] 9.5 [4.2, 14.8] **<0.001**	26

p value was calculated at each visit respect to the baseline value. LEI (Leeds Enthesitis Index), TJC (Tender Joint Count), SJC (Swollen Joint Count), PtGA (Patient Global Assessment), PGA (Physician Global Assessment), JUS (Joint Ultrasound Score), EUS (Enthesis Ultrasound Score), and JEUS (Joint and Enthesis Ultrasound Score).
Change, mean (SD), [CI95% mean], median[IQR], *p* value.

used to test the null hypothesis Ho: UIC = 20%. The Power of the test was also calculated.

The USS index was evaluated as a repeated measures study by adjusting a linear mixed model to evaluate changes between measurements and identify when the greatest reduction occurs.

For the secondary variables, the same analyses were used as for the primary variable. Regarding correlating changes in the ultrasound index and nail changes, scatter diagrams were drawn, and Spearman correlations were calculated, considering a value of .70 as acceptable. The same correlation analysis was performed with the ultrasound variables.

A type I error of 5% was established in the analysis. The values at each point were considered descriptive, and no adjustments were made for multiple comparisons. The analysis was conducted using the Stata 15.1 program.

To assess the agreement between observers, the weighted Kappa coefficient was calculated, with an average weighted kappa for all raters of 0.55.

Results

46 adult patients with PsA according to CASPAR criteria were included, and 26 of them (56.5%) finalized the study and were used for the final analysis. 20 patients were withdrawal, 14 in V1, 3 in V2 and 3 in V3. Reasons for withdrawal were lack of efficacy in 8 patients (17.4%), adverse events in 6 (13%), lost of follow up in 3 (6.5%) and inform consent withdrawal in 3 (6.5%).

The study population was composed by 19 women (41.3%) and 27 men (58.7%) with a mean age of 51.3 (10.4) years. Of the 46 patients participating, 45 were Caucasian (97.8%) and 1 was of another race (2.2%), year diagnosed with PsA: 2013.6 (4.7), uveitis 1 (2.2%), and dactylitis 24 (53.3%).

Personal medical history

The most frequent personal pathological antecedents were endocrinological in 14 patients (46.7%), Cardiovascular 12 (40%), Respiratory 4 (13.8%), Allergic 2 (6.9%), Hepatic 4 (13.8%), Gastrointestinal 5 (16.7%), Dermatologics 2 (6.9%), Urogenital 2 (6.9%), Endocrine 14 (46.7%), Hematologic 2 (6.9%), Psiquiatric 7 (24.1%).

Primary and secondary variable analysis. US index evaluation

Primary variable analysis

There was a 20% decrease in joint ($p = 0.006$) and total ($p < 0.001$) USS index 12 months after the introduction of Apremilast.

The mean value at the beginning and 12 m for JUS was 17.4 (SD 10.8) and 7.5 (SD 6.7), and for JEUS it was 23.4 (SD 12.4) and 10.7 (SD 7.6).

Secondary variable analysis

The study did not find a 50% or 70% reduction in USS index 12 months after the introduction of Apremilast.

All clinical parameters (LEI, TJC, SJC, PtGA, PGA, JUS, EUS, and JEUS) showed significant improvement between baseline and month 12 (see Table 1, Fig. 1).

Regarding the analytical parameters, the glomerular sedimentation rate and the C-reactive protein did not decrease significantly between baseline and month 12.

Correlation analysis

A strong correlation was observed between the ultrasound index change (UIC) and the swollen joint count (SJC), while moderate correlations were found between UIC and the tender joint count (TJC), patient global assessment (PtGA), physician global assessment (PGA), and C-reactive protein (CRP), as illustrated in Fig. 2.

Remission analysis

7 (26.92%) patients achieve clinical remission after 12 months of beginning apremilast. Clinical remission was considered when the sum of clinical variables were less than 5 (PGA, PtGA, LEI, TJC, SJC). Joint Ultrasound index (JUS) showed a difference between remission and no remission group (3 vs 9.2, $p < 0.032$), but these results aren't consistent due to a small number of dates of patients (7 vs 19) at the end (week 52). Others ultrasound index didn't show differences (Table 2).

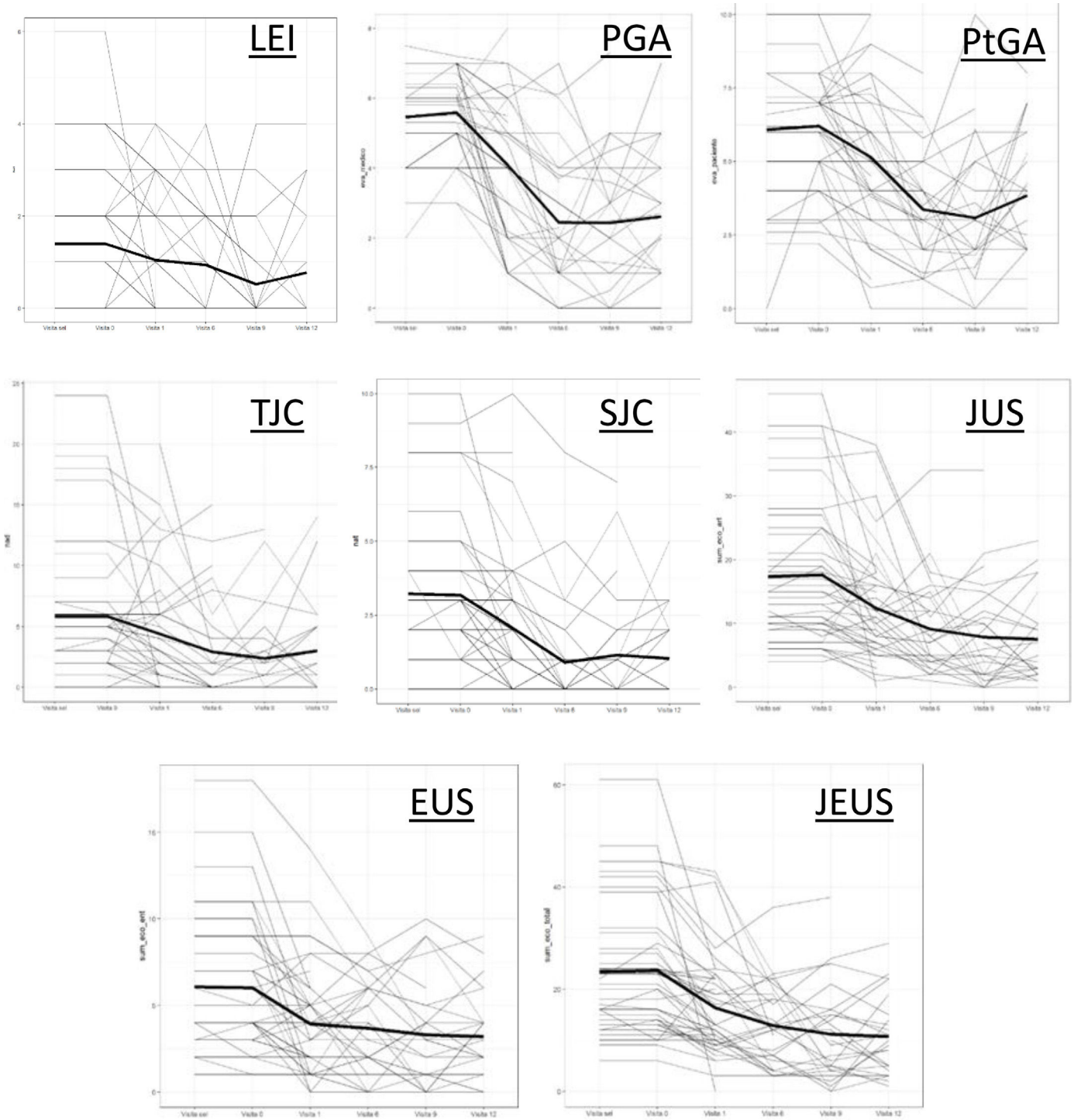

Fig. 1. The timeline evolution of clinical variables is depicted in figure. The results for clinical variables are presented in the graphics, where each line represents the evolution of a patient across different visits. The bold line indicates the mean value, providing an overview of the overall trend. LEI: Leeds enthesitis index. PGA: Physician global assessment. PtGA: patient global assessment. TJA: tender joint count. SJC: swollen joint count. JUS: joint ultrasound score. EUS: enthesitis ultrasound score. JEUS: joint and enthesis ultrasound score.

Additionally, we analyzed the relationship between remission at 52 weeks and ultrasound evaluation at the beginning of treatment. No results were obtained regarding being able to relate the ultrasound evaluation with obtaining clinical remission, except for LEI score. Results oriented to a possible biomarker for LEI score. Low results in LEI score at the beginning could predict Remission at 52 weeks (Table 2).

Evolution of nail ultrasound

Evolution of the ventral nail plate: due to the low sample size, the analysis of nail changes was conducted as exploratory. Therefore, we cannot conclusively determine whether the data are inconsistent with the clinical hypothesis.

Evolution of the nail subungueal thickness: we did not observe an improvement in the ventral ungueal parameters.

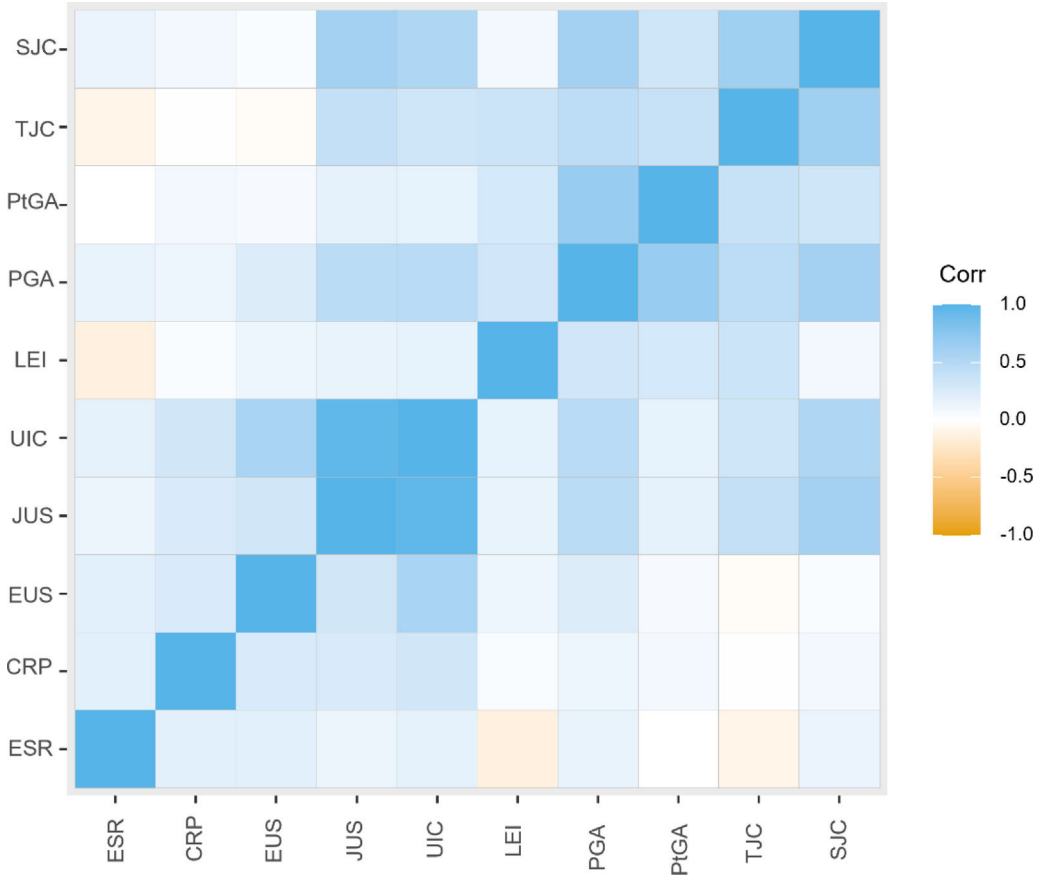

Fig. 2. Correlation between ultrasound indexes and clinical variables.

Comparison plate and thickness: the relationship between the ventral nail plate and thickness at each time point was evaluated. The comparison was conducted for fingers 2, 3, and 5 (without distinguishing between hands). The most severe category for nail plate changes and the average thickness were selected for analysis.

Despite the limited sample size, a significant relationship was observed between changes in the ventral nail plate and nail thickness ($p < 0.05$). However, due to the small sample size of the population, definitive conclusions cannot be drawn.

Onychopathy

Thickness: due to the low sample size, no changes were inferred, however a clinical relation between thickness and onychopathy was observed.

Nail plate: The data are not contradictory with clinical hypotheses, but no statistical evidence could be observed with the available sample size.

Safety management

The adverse events tables are presented according to MedDRA version 25.0 classification. During the clinical trial, a total of 81 adverse events occurred, with one classified as a serious adverse event (acute diverticulitis). The characteristics of the adverse events are summarized as follows: sixty (74%) were considered probably related to the study treatment, and twelve (14%) were considered possibly related to the study treatment. Additionally, sixty-three (77%) of the adverse events were of mild intensity, and thirteen (16%) were of moderate intensity.

The most frequent adverse event during the trial was diarrhea ($N = 16$; 19.75%), followed by respiratory tract infection ($N = 5$; 6.17%), dyspepsia ($N = 5$; 6.17%), nausea ($N = 4$; 4.93%), abdominal pain ($N = 3$; 3.7%), and depression ($N = 3$; 3.7%). No serious unexpected adverse event reactions (SUSARs) were reported during the trial.

Discussion

We enrolled 46 patients with active psoriatic arthritis in our study. Out of these, 26 patients completed the 12-month follow-up period. Primary endpoint, which was a 20% reduction in the ultrasound index for joint-enthesis involvement, was achieved successfully. Several secondary objectives demonstrated statistical significance, except for the 50% and 70% reduction in the ultrasound index, as well as the reduction in erythrocyte sedimentation rate (ERS) and C-reactive protein (CRP) levels at the 12-month mark.

This study demonstrates the efficacy of Apremilast in various domains of Psoriatic arthritis. We utilized a modified version of the Ficjan et al.[11] index to conduct our study, aiming to identify the most sensitive index for capturing changes in multiple psoriasis domains, including joints and entheses. Ceccarelli et al.[17] previously published a research paper utilizing a joint ultrasound index to study the efficacy of apremilast in PsA. They observed a significant reduction in their ultrasound index, which aligns with our findings. However, their study did not include the assessment of enthesis domain and nail manifestations. Our study highlights that Apremilast is an effective treatment across different domains, as evidenced by our novel ultrasound index. Recently, Torrente-Segarra et al.[18] have published a research study in 150 oligoarticular PsA patients. They demonstrated the utility of Apremilast in this

Table 2
Table shows relationship between remission at week 52 according with ultrasound variables at 52 weeks and at baseline.

Variable	Relation at 52 weeks			Relation 0 vs 52 weeks		
	Yes 27 (58.7%)	No 19 (41.3%)	*p*.value	Yes 27 (58.7%)	No 19 (41.3%)	*p*.value
PGA (0–10 cm)$_2$	7 0.6 (0.5) CI [0.1; 1.1] 1 [0, 1]	19 3.4 (1.6) CI [2.6; 4.1] 3 [2, 4.5]	<0.001	26 5.5 (1.2) CI [5; 6] 5.6 [4.2, 6.8]	19 5.7 (1.2) CI [5.1; 6.3] 6 [5, 7]	0.498
PtGA (0–10 cm)$_2$	7 1.7 (1) CI [0.8; 2.6] 2 [1.5, 2]	19 4.6 (1.9) CI [3.7; 5.5] 4.3 [3.5, 6]	0.001	26 6.4 (1.7) CI [5.7; 7.1] 7 [5, 7]	19 5.9 (2.2) CI [4.9; 7] 6 [4.5, 7.5]	0.537
LEI (0–6)$_2$	7 0.1 (0.4) CI [−0.2; 0.5] 0 [0.0]	19 1 (1.3) CI [0.4; 1.6] 0 [0.2]	0.142	26 1.1 (1.7) CI [0.4; 1.8] 0 [0, 1.8]	19 1.8 (1.4) CI [1.2; 2.5] 2 [1, 3]	0.031
TJC (0–28)$_2$	7 0.1 (0.4) CI [−0.2; 0.5] 0 [0, 0]	19 4.1 (4.2) CI [2; 6.1] 3 [0.5, 5.5]	0.007	26 5.8 (6.9) CI [3; 8.6] 3 [2, 6.5]	19 5.8 (4) CI [3.9; 7.8] 6 [4.5, 6]	0.151
SJC (0–28)$_2$	7 0 (0) CI [0; 0] 0 [0, 0]	19 1.4 (1.5) CI [0.7; 2.1] 2 [0, 2]	0.014	26 3.2 (2.3) CI [2.2; 4.1] 3 [2.3]	19 3.2 (2.5) CI [2; 4.4] 3 [1.5]	0.907
CRP (mg/dL)$_2$	7 0.3 (0.1) CI [0.2; 0.4] 0.2 [0.2, 0.4]	19 1.2 (1.9) CI [0.3; 2.2] 0.6 [0.2, 1.3]	0.385	26 1.8 (4) CI [0.1; 3.4] 0.4 [0.1, 1.4]	17 1.7 (3.2) CI [0; 3.3] 0.8 [0.1, 1.4]	0.765
JUS[a]	7 3 (2.4) CI [0.8; 5.2] 3 [1.5, 4]	19 9.2 (7) CI [5.8; 12.6] 9 [3, 14.5]	0.032	26 16.9 (11.2) CI [12.4; 21.4] 14.5 [9, 19]	19 18.6 (11) CI [13.3; 23.9] 18 [10, 25]	0.542
EUS[a]	7 3.6 (3.3) CI [0.5; 6.6] 2 [1.5, 5.5]	19 3.1 (2.2) CI [2; 4.1] 3 [1.5, 4]	0.93	26 5.3 (3.5) CI [3.9; 6.8] 4 [3, 7.8]	19 6.9 (4.2) CI [4.9; 9] 6 [4, 9.5]	0.151
JEUS[a]	7 6.6 (3.3) CI [3.5; 9.6] 8 [4, 8.5]	19 12.3 (8.2) CI [8.3; 16.2] 12 [4.5, 18.5]	0.111	26 22.3 (13.1) CI [17; 27.6] 21.5 [13, 24]	19 25.5 (12) CI [19.8; 31.3] 23 [15.5, 35.5]	0.259
ESR	7 10.1 (6.6) CI [4; 16.3] 8 [5, 13.5]	18 17.8 (13) CI [11.4; 24.3] 11.5 [8.2, 27.2]	0.236	25 18.5 (18.5) CI [10.8; 26.1] 10 [5, 33]	16 18 (14.1) CI [10.5; 25.5] 14 [6.8, 26.2]	0.521

Remission: sum of Swollen joint count (SJC), tender joint count (TJC), physician Disease State (PGA), patient disease State (PtGA), and LEI index.
[†]2: *N*.
Mean(sd).
[CI95% mean].
Median[IQR].
p.value: Mann–Whitney *U*.
[a] Joint Ultrasound count (JUS), tendon/enthesis Ultrasound count (EUS) and Joint enthesis Ultrasound count (JEUS).

subgroup of patients using the drug just after a classical DMARD for 6 months. But, like other authors, they focused on joint manifestation, but not on other domains like enthesis or nail.

We have demonstrated the utility of ultrasound in assessing the efficacy of a drug like Apremilast in patients with PsA. Based on these results, we believe it would be highly appropriate to use ultrasound for the assessment and monitoring of various domains of psoriatic disease. On the other hand, we know that the association of synovitis and enthesitis in PsA can predict the development of structural damage in the form of erosions.[19] By using imaging assessment indices that include other domains apart from joints, such as the entheses, tendons, and even the nails, we can aid in assessing the prognosis of our patients and fine-tune treatment to the maximum extent. In this regard, other authors have analyzed the utility of different treatments in joint involvement[20] and enthesitic involvement,[21] but they have done so without combining more than one type of involvement (joint or enthesis). The group of Grassi et al.[22] already advanced this strategy in their work, in which they defined an index called 5TPD. This index included joints, enthesis, tendon, skin, and nail domains. They demonstrated the utility of the index in assessing the effectiveness of anti-TNF alpha treatment in a group of patients with PsA, like what we have done with Apremilast.

Our study has the longest observation time using ultrasound in drug response measurement (12 months), and throughout the entire period, the various parameters have shown a significant reduction compared to baseline values.

We included patients with active PsA regardless of the clinical form, oligoarticular or polyarticular, according to clinical practice criteria. Our results show that apremilast can be effective in any clinical form of joint disease.

In our study, although this was not an initial objective, we observed clinical remission in 7 patients (26.92%). Remission was considered when the sum of different clinical parameters was less than 5, and there was an absence of inflammatory symptoms in both joint and other assessed domains, in line with what has been published in the literature, as documented in the article published by Mease PJ.[24] These results regarding clinical evaluation are more than we could expect, in relation to other recent studies. We observed a lower ultrasound index in the group of remission

patients than in the group of non-remission patients. In this group of patients, the ultrasound index was clearly lower than in patients not reaching remission (3 vs. 9.2, $p = 0.032$). But we can't consider these results as relevant due to the small number of patients to compare. Maybe it is necessary for a larger group to know if these findings are true or not.

Regarding nail involvement, we have not been able to obtain results with sufficient statistical power to draw reliable conclusions. The reason is the lack of sample size due to various technical problems in the centers. Despite this, and with the data we have, we observed a good correlation between nail involvement by ultrasound and clinical assessment. We know that onychopathy is a risk factor for the development of arthritis or enthesitis in patients with cutaneous psoriasis. Castellanos-Gonzalez et al.[23] analyzed 90 patients, of whom 61 had onychopathy, and of these, 31% (19/61) had Entesopathy compared to 13.8% (4/29) of those without nail involvement. They demonstrated the ability to predict Entesopathy using different NAPSI indices with a sensitivity and specificity of up to 69.6% and 59.7% ($p = 0.0001$). They also observed a correlation between the number of affected nails and the presence of Entesopathy ($p = 0.0035$). This is why we believe that this technique can be of great help in the early detection of subclinical onychopathy, thus assisting clinicians in suspecting a transition to PsA.

In terms of safety, we have not found any discordant evidence compared to previous publications. The most common adverse event, diarrhea, showed similar percentages to those reported in pivotal clinical trials and real clinical practice.

We acknowledge certain limitations in our study. Firstly, our sample can be considered small, 46 patients at the beginning and 26 at the end of the follow-up period. The results obtained have been statistically significant enough to present them. Both the design of the necessary sample and the subsequent analysis of the results make us affirm this fact. To date, this work is the one that has collected the largest population in an analysis of these characteristics. Despite all this, we believe that our results can be demonstrated in studies that manage to include a larger number of patients.

On the other hand, in the clinical evaluation, we did not include any specific disease activity scores. At the time of the study design, a fully consensual clinical index had not yet been established. Nowadays, we have several such as DAPSA or MDA, which help us monitor patients accurately. We utilized clinical assessment with individual parameters, and with this approach, we achieved results robust enough to communicate.

We did not include a placebo control group. While it is not statistically mandatory since we compare each patient's results against their own baseline, having a control group could potentially have provided clearer comparisons. However, due to ethical considerations regarding placebo treatment in a group of active PsAs patients, we opted not to conduct this type of study. It is worth noting that other research groups have also employed a similar strategy.[17,25]

Conclusions

Apremilast is an effective treatment for PsA patients. Ultrasound permit to identify the response in patients treated with it. Using a Joint-enthesis US index (USIC) we identified inflammatory changes at baseline and observed a significant improvement in all clinical variables, including the primary endpoint of 20% reduction in the USIC. Our findings confirm the utility of Apremilast as an optimal option for PsA patients. Indeed, it is important to highlight the usefulness of imaging techniques in the patient management of different treatment approaches in inflammatory arthropathies.

During the clinical trial, no important safety issues appeared, reaffirming the good safety profile of Apremilast.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability statement

The study data are available for consultation if considered necessary.

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References

1. Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsA-JAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S64–85.
2. Ory PA, Gladman DD, Mease PJ. Psoriatic arthritis and imaging. Ann Rheum Dis. 2005;64 Suppl. 2:55–7.
3. McQueen F, Lassere M, Østergaard M. Magnetic resonance imaging in psoriatic arthritis: a review of the literature. Arthritis Res Ther. 2006;8:1–8.
4. Filosa G, Grassi W, Kane D, Gutierrez M, De Angelis R, Filippucci E. A sonographic spectrum of psoriatic arthritis: "the five targets". Clin Rheumatol. 2009;29:133–42.
5. Grassi W, Gutierrez M. Psoriatic arthritis: need for ultrasound in everyday clinical practice. J Rheumatol. 2012;39 Suppl. 89:39–43.
6. Gandjbakhch F, Terslev L, Joshua F, Wakefield RJ, Naredo E, D'Agostino MA. Ultrasound in the evaluation of enthesitis: status and perspectives. Arthritis Res Ther. 2011;13:R188. Available from: http://arthritis-research.com/content/13/6/R188
7. Fiocco U, Ferro F, Vezzù M, Cozzi L, Checchetto C, Sfriso P, et al. Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept. Ann Rheum Dis. 2005;64:899–905.
8. De Agustín JJ, Moragues C, De Miguel E, Möller I, Acebes C, Naredo E, et al. A multicentre study on high-frequency ultrasound evaluation of the skin and joints in patients with psoriatic arthritis treated with inflximab. Clin Exp Rheumatol. 2012;30:879–85. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L368170162%5Cnhttp://www.clinexprheumatol.org/article.asp?a=5400%5Cnhttp://gerion.greendata.es:443/sfxlcl3?sid=EMBASE&issn=0392856X&id=doi:&atitle=A+multicentre+study+on+high-frequen
9. Husic R, Gretler J, Felber A, Graninger WB, Duftner C, Hermann J, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis. 2014;73:1529–36.
10. Aydin SZ, Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, et al. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. Ann Rheum Dis. 2013;72:992–5.
11. Ficjan A, Husic R, Gretler J, Lackner A, Graninger WB, Gutierrez M, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score). Arthritis Res Ther. 2014;16:1–13.
12. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol. 2015;42:479–88.
13. Huynh DQ, Kavanaugh A. Psoriatic arthritis: current therapy and future approaches. Rheumatol (United Kingdom). 2014;54:20–8.
14. Hansen RB, Kavanaugh A. Novel treatments with small molecules in psoriatic arthritis. Curr Rheumatol Rep. 2014;16:443.
15. Schafer PH, Parton A, Capone L, Cedzik D, Brady H, Evans JF, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. Cell Signal. 2014;26:2016–29. Available from: https://doi.org/10.1016/j.cellsig.2014.05.014
16. Costantino F, Carmona L, Boers M, Backhaus M, Balint PV, Bruyn GA, et al. EULAR recommendations for the reporting of ultrasound studies in rheumatic and musculoskeletal diseases (RMDs). Ann Rheum Dis. 2021;80:840–7.

17. Ceccarelli F, Lucchetti R, Perricone C, Spinelli FR, Cipriano E, Truglia S, et al. Musculoskeletal ultrasound in monitoring response to apremilast in psoriatic arthritis patients: results from a longitudinal study. Clin Rheumatol. 2019;38:3145–51.
18. Torrente-Segarra V, Bonet M. Apremilast use in oligoarticular psoriatic arthritis. J Rheumatol. 2022;49:1293–4.
19. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Nasr A. Tailored approach to early psoriatic arthritis patients: clinical and ultrasonographic predictors for structural joint damage. Clin Rheumatol. 2015;34:307–13.
20. Antonietta D'agostino M, Schett G, Ló Pez-Rdz A, Senolt L, Fazekas K, Burgos-Vargas R, et al. Response to secukinumab on synovitis using Power Doppler ultrasound in psoriatic arthritis: 12-week results from a phase III study, ULTIMATE. Rheumatology. 2022;61:1867–76. Available from: https://academic.oup.com/rheumatology [cited 18.7.23].
21. Litinsky I, Balbir-Gurman A, Wollman J, Arad U, Paran D, Caspi D, et al. Ultrasound assessment of enthesis thickening in psoriatic arthritis patients treated with adalimumab compared to methotrexate. Clin Rheumatol. 2016;35:363–70.
22. Gutierrez M, Di geso L, Salaffi F, Bertolazzi C, Tardella M, Filosa G, et al. Development of a preliminary US power Doppler composite score for monitoring treatment in PsA. Rheumatol (United Kingdom). 2012;51:1261–8.
23. Castellanos-González M, Joven BE, Sánchez J, Andrés-Esteban EM, Vanaclocha-Sebastián F, Romero PO, et al. Nagelbefall kann bei patienten mit psoriasis auf eine enthesiopathie hinweisen. J Ger Soc Dermatol. 2016;14:1102–8.
24. Mease PJ, Coates LC. Considerations for the definition of remission criteria in psoriatic arthritis. Semin Arthritis Rheum. 2018;47:786–96, http://dx.doi.org/10.1016/j.semarthrit.2017.10.021.
25. Lucchetti R, Ceccarelli F, Cipriano E, Perricone C, Spinelli FR, Alessandri C, et al. Application of ultrasound in the assessment of oligoarticular psoriatic arthritis subset: results from patients treated with apremilast. Isr Med Assoc J. 2021;23:412–5.