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ORIGINAL ARTICLE

Musculoskeletal ultrasound in monitoring response to apremilast in psoriatic arthritis patients: results from a longitudinal study

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Abstract

Introduction/objective Apremilast, PDE4 competitive inhibitor, has been recently introduced in the treatment of adult psoriatic arthritis (PsA) patients, but only preliminary data are available on imaging evaluation. Thus, we evaluated the response to apremilast in PsA patients by ultrasonographic (US) assessment.

Methods Thirty-four patients (M/F 7/27; median age 61 years, IQR 15; median disease duration 10 years, IQR 13) treated for polyarticular involvement were longitudinally evaluated. All the patients were assessed at baseline (T0), and after 6 (T1), 12 (T2), and 24 weeks (T3) by DAS28, CDAI, SDAI, and DAPSA. At the same time-points, US assessment was performed in 22 sites (wrists, MCPs, PIPs): synovial effusion/hypertrophy and power Doppler were scored with a semi-quantitative scale (0–3). A total score, corresponding to patient's inflammatory status, was obtained by their sum (0–198). We assessed also the presence of tenosynovitis of flexor $_{\text{tendons}}$ of hands' fingers bilaterally, registering the number of involved tendons (US-tenosynovitis score 0–10).

Results We found a significant reduction in the US inflammatory score values after 6 weeks (T0, median 15 (IQR 11.2); T1, 6 (10.0); $P = 0.0002$), confirmed at T2 (4.0 (4.0), $P = 0.0002$) and T3 (4.0 (6.0); $P = 0.0003$). Finally, US-detected tenosynovitis was observed in 44.1% of patients: a significant improvement in tenosynovitis score was identified at 6 weeks (T0, median 4 (IQR 4); T1, 1 (2); $P < 0.0001$) and maintained at T2 (0 (IQR 1); $P < 0.0001$) and T3 ((IQR 1.25); $P < 0.0001$).

Conclusions Apremilast is able to induce an early and sustained improvement of ultrasonographic inflammatory status at articular and peri-articular level.

Key points
•Apremilast induces a significant, early, and sustained improvement of inflammatory joint status in psoriatic arthritis patients.
•Ultrasonographic assessment is able to monitor articular and peri-articular response to apremilast.

Keywords Apremilast · Joint inflammation · Psoriatic arthritis · Treatment response · Ultrasonographic assessment

Introduction

Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease affecting 0.3–1.0% of the general population, leading to potential development of disability with significant impact on quality of life [1]. Current therapeutic options for PsA include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or biologic agents, with different molecular targets [2]. Recently, apremilast has been introduced in the treatment of adult PsA patients. It is a competitive inhibitor of phosphodiesterase 4 (PDE4) that acts by down-regulating intracellular inflammatory mediator synthesis by increasing cyclic adenosine monophosphate levels [3]. The efficacy and safety of this drug have been assessed by the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) programme, including four phase-three, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials [4–7].

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All the PALACE trials demonstrated the efficacy of apremilast in terms of ACR20 response after 16 weeks of treatment in patients naïve or previously treated by conventional and/or biological DMARDs [4–7]. More recently, the ACTIVE study analysed the early and sustained efficacy in biological-naïve patients, showing already after 2 weeks an ACR20 response in 16.4% of enrolled patients [8]. Besides articular involvement, PsA affects peri-articular structures, with the possible development of dactylitis and enthesitis. In the PALACE trials, a significant improvement of tendon involvement was observed, as demonstrated by the assessment of dactylitis score and Maastricht Ankylosing Spondylitis Enthesitis Score [9]. One of the most important limits of PALACE studies is certainly the lack of data about imaging assessment. As recommended by the EULAR task force, ultrasonography (US) with power Doppler is able to detect articular and peri-articular inflammation and may be used to monitor disease activity, providing additional information beside clinical and laboratory assessment also in PsA [10, 11].

We previously described a preliminary analysis on the significant improvement of US inflammatory score observed after 45 days of treatment with apremilast in PsA patients at articular level [12]. Thus, we longitudinally evaluated the US-detected efficacy of apremilast by analysing joint and tendon inflammatory status during 24 weeks of follow-up.

Materials and methods

In this prospective longitudinal study, we collected data about all consecutive PsA patients with polyarticular involvement and starting treatment with apremilast in agreement with Italian Agency of Drug (*Agenzia Italiana Farmaco—AIFA*) indication (active disease, with inadequate response or intolerance to at least 2 csDMARDs and contraindications or intolerance to bDMARDs), referring to the Arthritis Center of Sapienza University of Rome. PsA was diagnosed according to the Classification Criteria for Psoriatic Arthritis (CASPAR) [13]. Patients provided written informed consent at the time of the visit. The local ethical committee of "Policlinico Umberto I" of Rome approved the study.

After an initial dosage titration from day 1 to 5, apremilast was administered at the recommended maintenance dosage of 30 mg twice daily. At each visit, clinical and laboratory data were collected in a standardized, computerized, and electronically filled form, including demographics and past medical history with date of symptoms onset, co-morbidities, and previous and concomitant treatments.

According to study protocol, all patients underwent clinical and US assessment at the following time-points: baseline (T0), 6 weeks (T1), 12 weeks (T2), 24 weeks (T3). Clinical evaluation included tender and swollen joint counts (0–68) and visual analogue scale (VAS, 0–100, mm) for pain and global health assessment by the patient and the physician. Erythrocyte Sedimentation Rate (ESR, mm/h) and C Reactive Protein (CRP, mg/l) levels were also registered. Disease activity was calculated by means of disease activity score (DAS) in 28 joints by using ERS, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Disease Activity in Psoriatic Arthritis (DAPSA) [14–16].

Ultrasonographic assessment

US assessment was performed by a single rheumatologist sonographer (FCe), experienced in musculoskeletal US, who was blinded to the clinical and laboratory findings. A systematic multiplanar grey-scale and PD examination of 22 joints (bilateral I–V metacarpophalangeal, I–V proximal interphalangeal, wrist) was performed by using MyLab 70 XVisionGold (Esaote, Firenze, Italy) machine equipped with a multifrequency linear array transducer (6–18 MHz). The present study was conducted in a real-life setting, requiring a US assessment easy to perform and not time-consuming. Furthermore, the present study included PsA patients with polyarticular rheumatoid arthritis–like involvement. Thus, we decided to assess by US bilateral hand and wrist.

According to OMERACT definitions, the following inflammatory features were assessed: synovial effusion, synovial hypertrophy, power Doppler [17]. These elementary lesions were scored according to a semi-quantitative scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) and a total score (ranging from 0 to 198), corresponding to the patient's inflammatory status at joint level obtained by their sum.

Moreover, the protocol included US evaluation at level of flexor $_{\text{tendons}}$ of hands' fingers bilaterally, by multiplanar longitudinal and transverse scanning from the palm of the hand to

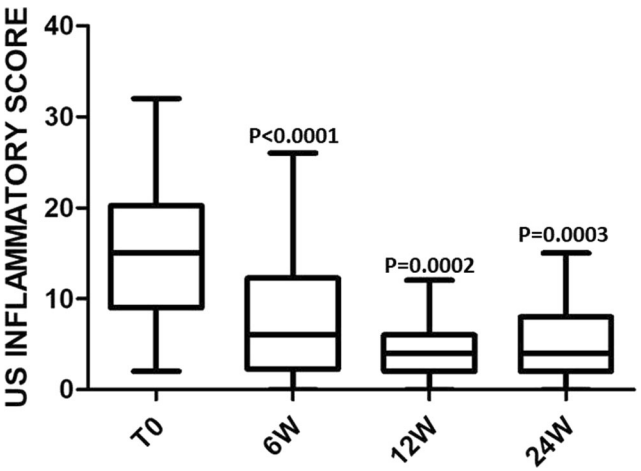


Fig. 1 Box and whiskers plot (median, quartiles, range) of US inflammatory score of 34 PsA patients at baseline (T0, $N = 34$) and after 6 (T1, $N = 30$), 12 (T2, $N = 28$), 24 weeks (T3, $N = 28$) of treatment with apremilast. *P* values were referred to the comparison with baseline

Table 1 Median (IQR) values of composite indices evaluated at T0 (baseline), T1 (6 weeks), T2 (12 weeks), T3 (24 weeks) in PsA patients

Clinimetric indices	T0	T1	T2	T3	*P* value
DAS28*	4.6 (1.7)	4.1 (1.5)	3.7 (1.8)	3.7 (1.7)	T0 vs T1 $P = 0.001$
					T0 vs T2 $P < 0.0001$
					T0 vs T3 $P = 0.0001$
CDAI*	22.5 (11.2)	16.2 (5.5)	12.5 (9.6)	13.0 (6.0)	$P < 0.0001$
					for all comparisons
SDAI*	24.1 (14.4)	16.2 (6.7)	15.0 (10.0)	13.3 (9.2)	T0 vs T1 $P = 0.0001$
					T0 vs T2 $P < 0.0001$
					T0 vs T3 $P < 0.0001$
DAPSA*	26.5 (14.0)	19.0 (10.4)	16.7 (12.4)	15.7 (7.4)	T0 vs T1 $P = 0.002$
					T0 vs T2 $P < 0.004$
					T0 vs T3 $P < 0.0008$

DAS28 disease activity score in 28 joints calculated with ESR, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *DAPSA* Disease Activity in Psoriatic Arthritis

the distal phalanx. According to the OMERACT definitions, tenosynovitis was defined as "presence of hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit PD signal" [17]. The presence of tenosynovitis at level of bilateral I–V fingers flexor tendons was registered with a dichotomous score (0 = absent, 1 = present), obtaining a total tenosynovitis score ranging from 0 to 10.

Statistical analysis

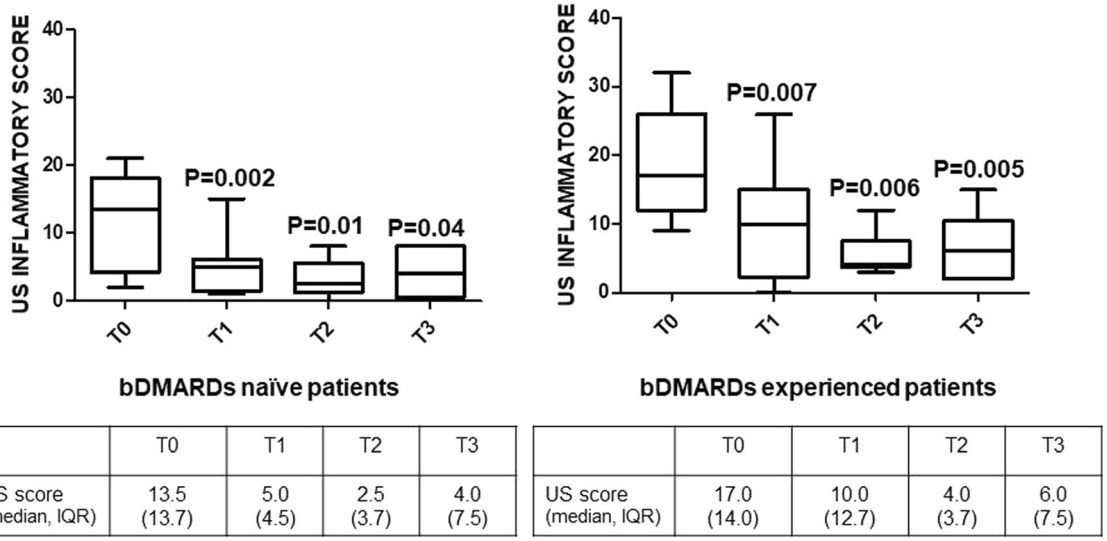
Statistical analysis was performed using SPSS statistical software, version 13.0 (SPSS, Chicago, IL, USA). Quantitative variables (DAS-28, CDAI, SDAI, DAPSA, US total score, US-tenosynovitis score) were given as the median and interquartile range (IQR).

The comparisons between parametric variables were performed with the Wilcoxon's test. Pearson's and Spearman's tests were used to perform the correlation analysis. *P* values < 0.05 were considered statistically significant.

Results

Since April 2017, 50 PsA patients started treatment with apremilast. Among these, a polyarticular involvement was observed in 34 subjects (M/F 7/27; median age 61 years, IQR 15; median disease duration 10 years, IQR 13). The present analysis was carried out on these patients.

According to AIFA indication, 11 patients (32.4%) were treated by apremilast due to high infective risk; 9 (26.5%) due to previous recent—less than 5 years—malignancy; 6



	T0	T1	T2	T3
US score (median, IQR)	13.5 (13.7)	5.0 (4.5)	2.5 (3.7)	4.0 (7.5)

	T0	T1	T2	T3
US score (median, IQR)	17.0 (14.0)	10.0 (12.7)	4.0 (3.7)	6.0 (7.5)

Fig. 2 Box and whiskers plot (median, quartiles, range) of US inflammatory score of naïve or bDMARD-experienced PsA patients at baseline (T0) and after 6 (T1), 12 (T2), 24 weeks (T3) of treatment with apremilast. *P* values were referred to the comparison with baseline

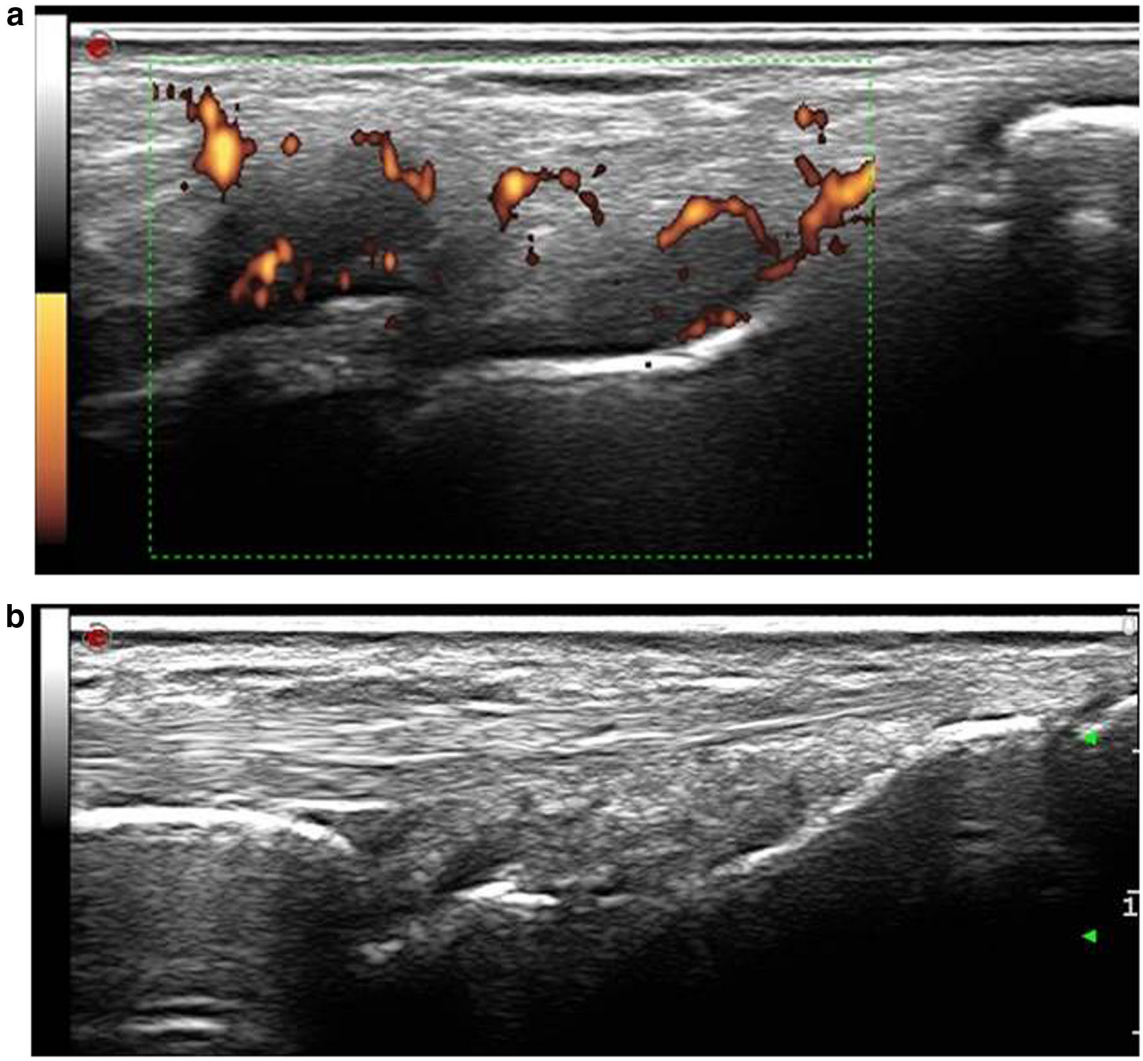


Fig. 3 Representative image showing the modifications of US assessment at level of radiocarpal joints at baseline (**a**) and after 12 weeks of treatment (**b**) with apremilast. In **a**, an active synovitis (with positivity for power Doppler); **b** documented the resolution of this inflammatory status during treatment

(17.6%) for biological DMARD intolerance; 2 (5.9%) for the concomitant presence of an autoimmune disease; 2 (5.9%) for concomitant demyelinating disease; and 4 (11.7%) for other conditions (NYHA class III–IV, needle phobia).

Sixteen patients (47.0%) were previously treated with at least one biological DMARD: among these, 50% were resistant to these drugs. Apremilast was administered in association with other synthetic DMARDs in 14 patients (41.2%: 6 with sulphasalazine, 4 with methotrexate, 2 hydroxychloroquine, 2 leflunomide); moreover, 15 patients (44.1%) were assuming glucocorticoid treatment (median daily dosage 5 mg, IQR 0).

During follow-up, 4 patients (11.7%) discontinued apremilast due to gastrointestinal side effects (diarrhoea and nausea) and 2 (5.9%) for lack of efficacy after a median of 2.5 months (IQR 2.75 months). Moreover, 10 patients (29.4%) experienced prolonged diarrhoea leading to a reduction of drug dosage to 30 mg daily. US assessment demonstrated a significant reduction in the median values of joint inflammatory score already after 6 weeks of treatment (T0 median 15 (IQR 11.2) versus T1 6 (10.0); $P = 0.0002$; Fig. 1). Such statistically significant improvement was maintained at the following time-points (T2 4.0 (4.0); T3 4.0 (6.0); T0 versus T2 $P = 0.0002$; T0 versus T3 $P = 0.0003$; Fig. 1).

Similar to US inflammatory score, a significant reduction was registered for all the composite indices evaluated in our cohort (Table 1). At baseline, we found a significant correlation between US inflammatory score and DAS28 ($r = 0.4$, $P = 0.01$), CDAI ($r = 0.5$, $P = 0.003$), and SDAI ($r = 0.4$, $P = 0.01$). We separately analysed patients according to previous treatment with biological DMARDs in terms of US-detected improvement. At baseline, US inflammatory score was significantly higher in biological DMARDs experienced (median 17, IQR 14) in comparison with naïve patients (median 13.5,

Table 2 Changes in clinimetric indices during treatment with apremilast in patients naïve or previously experienced bDMARDs. All values are expressed as median (IQR)

Clinimetric indices*	T0	T1	T2	T3	*P*
bDMARD naïve					
DAS28	4.6 (1.3)	3.7 (1.7)	3.6 (1.1)	3.1 (1.1)	T0 vs T1 $P = 0.01$
					T0 vs T2 $P = 0.002$
					T0 vs T3 $P = 0.01$
CDAI	21 (7.1)	15 (7.5)	10 (10.0)	11 (9.0)	T0 vs T1 $P = 0.002$
					T0 vs T2 $P = 0.0006$
					T0 vs T3 $P = 0.001$
SDAI	23.1 (9.3)	15.6 (8.4)	18.7 (11.8)	11.4 (12.2)	T0 vs T1 $P = 0.006$
					T0 vs T2 $P = 0.002$
					T0 vs T3 $P = 0.001$
DAPSA	26.5 (10.2)	15.4 (9.6)	9.7 (12.0)	12.2 (7.5)	T0 vs T1 $P = 0.01$
					T0 vs T2 $P = 0.01$
					T0 vs T3 $P = 0.01$
bDMARD experienced					
DAS28	5.4 (1.8)	5.2 (1.6)	5.2 (0.8)	4.7 (0.6)	T0 vs T1 $P = 0.04$
					T0 vs T2 $P = 0.005$
					T0 vs T3 $P = 005$
CDAI	25 (18.0)	18 (18.0)	14 (8.0)	14 (3.0)	T0 vs T1 $P = 0.04$
					T0 vs T2 $P = 0.02$
					T0 vs T3 $P = 0.02$
SDAI	29.5 (20.4)	18.3 (9.4)	20.8 (6.9)	18.4 (5.1)	T0 vs T1 $P = 0.01$
					T0 vs T2 $P = 0.02$
					T0 vs T3 $P = 0.02$
DAPSA	37.2 (18.5)	28.5 (9.2)	26	26.4 (7.4)	T0 vs T1 P = NS
			(14.2)		T0 vs T2 P = NS
					T0 vs T3 P = NS

DAS28 disease activity score in 28 joints, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *DAPSA* Disease Activity in Psoriatic Arthritis

IQR 13.7, $P = 0.04$). As represented in Fig. 2, in both groups, a significant reduction in US inflammatory score was demonstrated (Fig. 2).

Figure 3 shows a representative image showing the modifications of US assessment during treatment with apremilast.

Furthermore, we found a significant improvement in all composite indices at different time-points evaluated in biological-naïve patients; conversely, in previously treated patients, we found a significant improvement in all indices except for DAPSA (Table 2). At clinical examination, none of the patients showed a dactylitis at study entry. Conversely, US assessment identified the presence of tenosynovitis in 15 patients (44.1%), with a median score of 4 (IQR 4). As reported in Fig. 4, we found a significant improvement in US-tenosynovitis score after 6 weeks of treatment (T1 median 1 (IQR 2), $P < 0.0001$), confirmed at the following time-points (T2 median 0 (IQR 1), $P < 0.0001$; T3 median 0 (IQR 1.25), $P < 0.0001$).

Finally, we performed a sub-analysis by classifying PsA patients according to the concomitant treatment with glucocorticoids (GCs). In terms of clinical response, a significant improvement of DAS28 values was identified in all time-points evaluated irrespective to the concomitant treatment with GCs. In terms of US inflammatory score, patients treated by GCs $_{\text{showed}}$ a significant reduction of US score at T1 (T0 median 16.0 (IQR 15) versus 6 (11.5), $P = 0.001$) that was maintained at T2 (4 (3), $P = 0.0006$) and T3 (4 (6), $P = 0.0009$). When considering patients without concomitant GC treatment, a significant reduction of US score was identified at T1 (14 (9.7) versus 6 [9], $P = 0.0004$) and T2 (3 (5), $P = 0.04$).

Discussion

In the present study, specifically designed to evaluate the US-detected efficacy of apremilast in PsA patients in a real-life setting, we demonstrated a significant, early, and sustained improvement of inflammatory joint status at articular and peri-articular level.

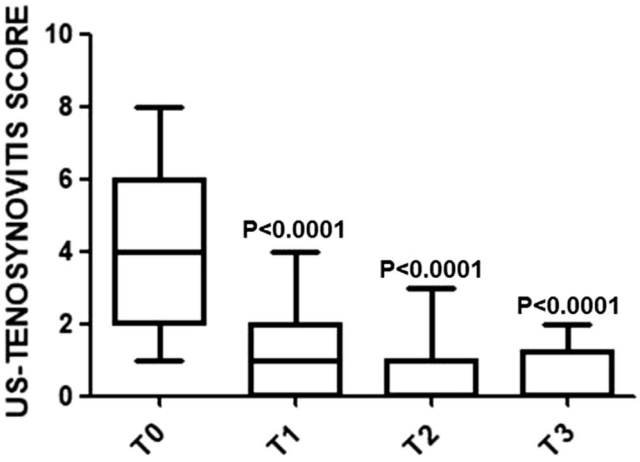


Fig. 4 Box and whiskers plot (median, quartiles, range) of US tenosynovitis score in PsA patients at baseline (T0) and after 6 (T1), 12 (T2), 24 weeks (T3) of treatment with apremilast. *P* values were referred to the comparison with baseline

In spite of several data deriving from RCTs on apremilast efficacy, very few data are available concerning its use in clinical practice. Abignano and colleagues published a retrospective report describing 71 unselected PsA patients [18]. In this study, disease activity and treatment response were assessed at 6 months according to the treating clinician's judgement: specifically, absence of peripheral arthritis, enthesitis, and dactylitis on clinical examination, or improvement of clinical signs at physical examination and concurrent patient's reported improvement of symptoms as per PsA response criteria. According to these criteria, 60.8% of patients were classified as responders [18]. Despite the EULAR recommendations about the use of imaging tools in the assessment of PsA patients, RCTs leading to apremilast approval did not include this aspect in the drug response evaluation [4–8]. As widely demonstrated, US shows a higher sensitivity in the assessment of joint inflammatory status in comparison with physical evaluation, as confirmed by the evidence of a US-detected subclinical synovitis [19]. Moreover, a disconnection between US features and clinical findings has been documented [20]; recently, Ruta and colleagues identified the presence of US-detected synovitis in 37% of PsA patients in clinical remission [21]. According to these evidences, we included US assessment as part of a comprehensive evaluation of PsA patients in our real-life setting.

We previously reported our experience in the first 13 polyarticular PsA patients treated by apremilast. The drug was able to promptly reduce the articular inflammatory status, as demonstrated by the significant reduction of US score after 45 days (6 weeks) of treatment [12]. In the present study, we confirmed these results in a larger cohort of PsA patients; moreover, the early response was maintained at 24 weeks of follow-up. US assessment demonstrated the efficacy of apremilast regardless of previous treatment with biological DMARDs: in fact, a significant improvement in US inflammatory score was demonstrated in naïve patients but also in those who previously experienced treatment.

Furthermore, moving from the disease heterogeneity, characterized by extra-articular involvement, we also assessed tendon involvement, focusing on tenosynovitis.

By a clinical point of view, RCTs have previously demonstrated the efficacy of apremilast on extra-articular involvement. The pooled analysis of PALACE 1, 2, and 3 demonstrated a significant improvement in dactylitis score, obtained from the count of clinically evident dactylitis in each of the 20 digits [9]. Of note, dactylitis was reported in 38.7–44.6% of patients but data about the punctual prevalence in polyarticular subset were not available [9].

The evaluation of US-detected inflammatory changes at level of tendon, in particular tenosynovitis, has been performed in patients affected by inflammatory arthritis. Recently Tinazzi and colleagues identified this condition in 38% of patients in a PsA cohort, a significantly higher prevalence than in rheumatoid arthritis patients [22].

We assessed the presence of tenosynovitis in our PsA cohort, showing a significant and early improvement of US-tenosynovitis score, maintained at 24 weeks of follow-up. This result confirms the ability of apremilast to improve not only articular involvement but also peri-articular structures that are frequently involved in PsA patients.

The main limitation of our report is the limited number of PsA patients evaluated. Moreover, the follow-up of our analysis should be prolonged in order to reach solid conclusions about the efficacy of the apremilast treatment. Nonetheless, we provided the evidence about the ability of apremilast to induce a prompt and sustained improvement in the US-detected articular and peri-articular inflammatory status of PsA patients.

In conclusion, apremilast was able to induce an early and sustained improvement of US-detected inflammatory status at articular and peri-articular level confirming. These results confirmed the ability of US assessment in the evaluation of treatment response.

Compliance with ethical standards Patients provided written informed consent at the time of the visit. The local ethical committee of "Policlinico Umberto I" of Rome approved the study.

Disclosures None.

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