# Application of Ultrasound in the Assessment of Oligoarticular Psoriatic Arthritis Subset: Results from Patients Treated with Apremilast

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**ABSTRACT** **Background:** Psoriatic arthritis (PsA) is an inflammatory rheumatic disease characterized by different phenotypes in terms of joint involvement. The so-called oligoarticular pattern involves fewer than five active joints at a different time points. The evaluation of disease activity in this subset of patients is an unmet need due to the lack of specific indices able to capture modifications over time.

**Objectives:** To evaluate the ability of musculoskeletal ultrasound to monitor the response to apremilast treatment in oligoarticular PsA patients.

**Methods:** We evaluated 24 oligoarticular patients (19 women, 5 men; median age 56 years, interquartile range (IQR) 19; median disease duration 5 years, IQR 5.75). All patients were assessed at baseline (T0), and after 6 (T1), 12 (T2), and 24 (T3) weeks. Clinical assessment included evaluation of 66 swollen joints and patient global health assessment. All the patients underwent ultrasound assessment of the clinically involved joints. Synovial effusion/hypertrophy and power Doppler were scored with a semi-quantitative scale (0–3). The total inflammatory score was the sum of these scores.

**Results:** We found a reduction in the ultrasound inflammatory score at all time points, with a significant improvement at 6 and 12 weeks of treatment compared with baseline: T0 median 8.5 (IQR 5.0); T1 3.5 (3.0); T2 2.0 (3.5); $P = 0.01$. We observed a significant reduction of patient global health assessment after 24 weeks (T0 median 50 (32.5); T3 40 (57.5); $P = 0.01$).

**Conclusions**: Musculoskeletal ultrasound could be useful in the assessment of treatment response in PsA patients with oligoarticular subset.

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**KEY WORDS:** apremilast, musculoskeletal ultrasound, oligoarticular involvement, psoriatic arthritis (PsA), treatment response

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Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease affecting 0.3–1.0% of the general population. PsA can lead to development of disability with significant impact on quality of life [1,2]. Current treatments include traditional synthetic and biologic agents with possible different clinical response depending on different factors [3].

Updated treatment and classification guidelines identified six disease domains: peripheral arthritis, enthesitis, dactylitis, spondylitis, skin, and nail psoriasis [2,4].

Classically, PsA can be categorized into five clinical phenotypes according with joint involvement: symmetrical polyarthritis, asymmetrical oligoarthritis and monoarthritis, mutilans arthritis, distal interphalangeal predominant (DIP) joint, and predominant spondyloarthritis [5]. Oligoarthritis PsA, identified in 13–65% of PsA patients, is defined as the involvement of fewer than five active joints at different time points [6]. This phenotype seems to be less aggressive in terms of erosive damage. It is commonly reported in early disease stages and sometimes can progress to the polyarticular pattern [7].

The assessment of oligoarticular PsA is still considered an unmet need in the rheumatology field. Indeed, the evaluation of disease activity is not well defined. Generally, oligoarticular pattern was evaluated by using the same indices applied for the polyarticular phenotype. However, oligoarticular PsA patients cannot be accurately assessed using reduced joint counts designed for rheumatoid arthritis due to the possibility to miss active joints, especially in patients with predominant lower limbs or distal interphalangeal joints involvement [8]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the Outcome Measures in Rheumatology recommend to evaluate 66\68 joints to assess the presence of swollen and tender joints, respectively [9,10].

Recently, apremilast, a competitive inhibitor of phosphodiesterase 4, has been introduced as a treatment for adult PsA patients [11]. In the registration trials, some data are available about the drug efficacy in oligoarticular subset, but no specific indices have been applied to evaluate this disease subset [12-15]. Thus, in the present longitudinal study we investigated the abili-

ty of musculoskeletal ultrasound to assess an oligoarticular PsA cohort treated by apremilast.

## PATIENTS AND METHODS

In this prospective longitudinal study, we collected data on consecutive PsA patients with oligoarticular involvement and starting treatment with apremilast in agreement with the Italian Agency of Drug−Agenzia Italiano Farmaco (AIFA), who were referred to the Arthritis Center of Sapienza University of Rome, from April 2017. PsA was diagnosed according to the Classification Criteria for Psoriatic Arthritis (CASPAR) [2]. Patients provided written informed consent at the time of the visit. The local ethics 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. All patients underwent clinical and ultrasound assessment in the clinically involved joints at the following time-points: baseline (T0), 6 weeks (T1), 12 weeks (T2), and 24 weeks (T3). Clinical evaluation included swollen joint counts (0–66) and visual analogue scale (VAS, 0–100, mm) for pain and global health assessment by the patient (GHpt) and the physician (GHph). Erythrocyte sedimentation rate (ESR, mm/h) and C-reactive protein (CRP, mg/l) levels were also registered.

### ULTRASONOGRAPHIC ASSESSMENT

Ultrasound assessment was performed by a single rheumatologist sonographer (FCe), experienced in musculoskeletal ultrasound, who was blinded to the clinical and laboratory findings. A systematic multiplanar grey-scale and PD examination of each joint clinically involved was performed by using a MyLab Eight Exp (Esaote, Florence, Italy) machine equipped with a multifrequency linear array transducer (6–18 MHz). According to OMERACT definitions, the following inflammatory features were assessed: synovial effusion, synovial hypertrophy, and power Doppler [16]. In particular, synovial effusion was defined as abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible but does not exhibit Doppler signal. Synovial hypertrophy, as abnormal hypoechoic intra-articular tissue, is not displaceable and poorly compressible, which may exhibit Doppler signals [16]. Thus, synovial effusion, synovial hypertrophy, and power Doppler were scored according to a semi-quantitative scale ranging from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) and a total score was obtained by their sum, corresponding to the patient's inflammatory status. Furthermore, in patients with clinical hands involvement, the study protocol included ultrasound evaluation at level of flexor tendons of fingers bilaterally, by multiplanar longitudinal and transverse scanning from the palm of the hand to 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 [16]. The presence of tenosynovitis at the level of finger flexor tendons was registered with a dichotomous score (0 = absent, 1 = present). Last, in patients with clinical signs of enthesitis, ultrasound was performed to assess Doppler signals at the entheseal site.

### STATISTICAL ANALYSIS

Statistical analysis was performed using GraphPad Prism statistical software, version 8.0 (GraphPad Inc., San Diego, CA, USA). Quantitative variables (swollen joint counts, VAS pain, GHpt, GHph, and ultrasound total 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

The present analysis included 24 patients. Their clinical and demographic features are shown in Table 1. According to AIFA indication, 9 patients (37.5%) were treated by apremilast due to high infective risk; 6 (25.0%) due to previous recent (less than 5 years) malignancy; 3 (12.5%) for hypertransaminasemia; 2 (8.3%) for biological DMARDs intolerance; 1 (4.2%) for concomitant demyelinating disease; 1 (4.2%) for inefficacy of anti-TNF and anti-IL-17 treatment; and 2 (8.3%) for other conditions (needle phobia, anorgasmia). During follow-up, one patient (4.2%) discontinued apremilast due to gastrointestinal side effects (diarrhea and nausea), two patients (8.3%) for headache, one patient for general malaise, and four (16.7%) for lack of efficacy after a median of 2.5 months (IQR 2.75).

Table 2 shows data about the joint assessment in our PsA cohort. At baseline, we found a median swollen joint count of 1.0 (IQR 2.0). Specifically, 11 patients (45.8%) showed the involvement of a knee, 6 (25.0%) of ankle, 4 (16.7%) of hand, 3 (12.5%) of wrist, and 3 (12.5%) of feet. These joints were assessed by ultrasound. Furthermore, 5 patients (20.8%) showed dactylitis at hands level and 4 (16.7%) enthesitis (2 at knee level, medial condyle femur; 2 at Achilles tendon).

The median count of swollen joints remained unchanged during the follow-up. Conversely, we found a significant reduction for GHpt after 24 weeks of treatment (T0 versus T3, $P = 0.01$). No significant improvement was found for pain VAS.

### ULTRASOUND ASSESSMENT IN CLINICALLY INVOLVED JOINTS

At baseline we found a median inflammatory score of 8 (IQR 5.0). We found a decrease of this score at T1 (median 3.5, IQR 3.0, P = 0.01), T2 (median 2.0, IQR 3.5, P = 0.01), and T3 (median 0.0, IQR 4.5, P = NS). These results are represent-

**Table 1.** Clinical and demographic features of the 24 oligoarticular PsA patients included in the present study

| Characteristic | Value |
|---|---|
| **N** (%) | 24 (34.3) |
| **Sex** (female/male) | 19/5 |
| **Age**, years (median, IQR) | 56, 19 |
| **Disease duration**, years (median, IQR) | 5, 5.75 |
| **Psoriasis**, n (%) | 19 (79.2) |
| **Dactylitis**, n (%) | 8 (33.3) |
| **Enthesitis**, n (%) | 4 (16.7) |
| **Nail dystrophy**, n (%) | 7 (29.2) |
| **Previous biologic**, n (%) | 8 (33.3) |
| **Concomitant csDMARDs treatment** | 11 (45.8) |
| Sulfasalazine, n (%) | 5 (45.5) |
| Methotrexate, n (%) | 4 (36.4) |
| Hydroxychloroquine, n (%) | 2 (18.2) |
| Leflunomide, n (%) | 0 |
| Cyclosporine, n (%) | 0 |
| **Concomitant GC treatment**, n (%) | 8 (33.3) |

csDMARDs = conventional synthetic desease modifying anti-rheumatic drugs, GC = glucocorticoids, IQR = interquartile range, PsA = psoriatic arthritis

ed in Figure 1. All the patients with clinical dactylitis showed ultrasound-detected tenosynovitis, with a median count of 1 (IQR 1) that significantly reduced at 12 weeks (T3: median 0, IQR 0, P = 0.004) and 24 weeks (T4: median 0, IQR 0, P = 0.004). Finally, two PsA patients showed Doppler signals at Achilles tendon levels that disappeared after 6 weeks (T1) of treatment and remained unchanged at T2 and T3 time points.

## DISCUSSION

We evaluated the ability of ultrasound to assess treatment response in a PsA cohort with oligoarticular subset, treated by apremilast. Thus, we observed the improvement of articular and periarticular involvement differently from other clinical parameters applied in our analysis.

Evidence has shown that musculoskeletal ultrasound has a higher sensitivity in the assessment of articular and periarticular inflammatory status compared to physical evaluation, as underlined by the presence of an ultrasound-detected subclinical synovitis in remitted patients [17-19]. However, the classification of PsA can be changed when considering the ultrasound assessment, since detection of asymptomatic inflammation by imaging techniques could result in reclassification of patients from oligoarticular to polyarticular PsA [20,21].

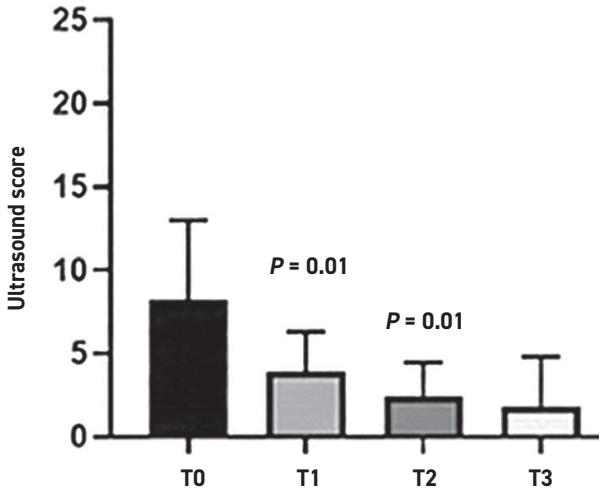
Despite oligoarticular PsA subset is generally considered less severe than polyarticular disease, multiple domains could be involved in this disease phenotype. In particular, in these PsA patients it is possible the identification of dactylitis and enthesitis [8]. Of note, one study reported a higher prevalence of axial symptoms, dactylitis, and co-morbidities in oligoarticular PsA compared to polyarticular PsA [22]. Moreover, the lack of specific tools able to evaluate disease activity in oligoarticular PsA could make the choice of an appropriate therapeutic approach difficult.

**Table 2.** Median values of parameters considered in the evaluation of 24 oligoarticular PsA patients enrolled in the study

| | T0 | T1 | T2 | T3 | *P* value |
|---|---|---|---|---|---|
| **Swollen joints (median, IQR)** | 1.0, 2.0 | 1.0, 1.8 | 1.0, 2.0 | 1.0, 1.0 | T0 versus T1; *P* = NS<br>T0 versus T2; *P* = NS<br>T0 versus T3; *P* = NS |
| **VAS pain (median, IQR)** | 50.0, 32.5 | 45.0, 48.8 | 65.0, 48.8 | 40.0, 57.5 | T0 versus T1; *P* = NS<br>T0 versus T2; *P* = NS<br>T0 versus T3; *P* = NS |
| **GHpt (median, IQR)** | 50.0, 32.5 | 50.0, 38.8 | 60.0, 47.5 | 40.0, 57.5 | T0 versus T1; *P* = NS<br>T0 versus T2; *P* = NS<br>T0 versus T3; *P* = 0.01 |
| **GHph (median, IQR)** | 40.0, 27.5 | 40.0, 15.0 | 50.0, 30.0 | 30.0, 42.5 | T0 versus T1; *P* = NS<br>T0 versus T2; *P* = NS<br>T0 versus T3; *P* = NS |

GHpt = global health assessment by the patient, GAph = global health assessment by the physician, IQR = interquartile range, PsA = psoriatic arthritis, VAS = visual analogue scale
T0 = baseline, T1 = after 6 weeks, T2 = after 12 weeks, T3 = after 24 weeks

**Figure 1.** Median values of ultrasound inflammatory score at different time-points (Box Whiskers plot representation)




Based on this evidence, we propose the inclusion of musculoskeletal ultrasound assessment in the context of a comprehensive evaluation of PsA patients in a real-life setting.

We previously reported our experience on ultrasound assessment in PsA patients with polyarticular subset, treated by apremilast: this imaging technique was able to capture the improvement of inflammatory status [23,24].

We observed the ability of ultrasound to capture the changes in articular and peri-articular inflammatory status of patients with oligoarticular pattern, unlike the other indices used in this analysis. In fact, we identified the reduction of joint ultrasound score, parallel to the improvement in tenosynovitis and enthesitis. Thus, we suggest the application of this technique in the management of oligoarticular PsA in order to evaluate drug efficacy.

## LIMITATIONS

The main limitation of our report is the limited number of PsA patients included.

## CONCLUSIONS

Ultrasound can capture the change of joint inflammatory status in apremilast-treated patients. In particular, ultrasound can overcome the limits of clinical evaluation in oligoarticular subset, which contributes to the redefinition of disease activity.

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## REFERENCES

1. Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973; 3 (1): 55-78.
2. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54 (8): 2665-73.
3. Generali E, Sciré CA, Cantarini L, Selmi C. Sex Differences in the treatment of psoriatic arthritis: a systematic literature review. *IMAJ* 2016; 18 (3-4): 203-8.
4. Iannone F, Lopalco G, Rigante D, Orlando I, Cantarini L, Lapadula G. Impact of obesity on the clinical outcome of rheumatologic patients in biotherapy. *Autoimmun Rev* 2016; 15 (5): 447-50.
5. Dhir V, Aggarwal A. Psoriatic arthritis: a critical review. *Clin Rev Allergy Immunol* 2013; 44 (2): 141-8.
6. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med* 2017; 376 (10): 957-70.
7. Eder L, Gladman DD. Psoriatic arthritis: phenotypic variance and nosology. *Curr Rheumatol Rep* 2013; 15 (3): 316.
8. Coates LC, FitzGerald O, Gladman DD, et al. Reduced joint counts misclassify patients with oligoarticular psoriatic arthritis and miss significant numbers of patients with active disease. *Arthritis Rheum* 2013; 65 (6): 1504-9.
9. Gladman DD, Mease PJ, Strand V, et al. Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 2007; 34 (5): 1167-70.
10. Lubrano E, Cantini F, Costanzo A, et al. Measuring psoriatic disease in clinical practice. An expert opinion position paper. *Autoimmun Rev* 2015; 14 (10): 864-74.
11. Schafer PH, Parton A, Capone L, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal* 2014; 26: 2016-29.
12. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014; 73: 1020-26.
13. Cutolo M, Myerson GE, Fleischmann RM, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol* 2014; 43 (9): 1724-34.
14. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis* 2016; 75: 1065-73.
15. Wells AF, Edwards CJ, Kivitz AJ, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. Rheumatology (Oxford) 2018; 57 (7): 1253-63.
16. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-87.
17. Iagnocco A, Ceccarelli F, Perricone C, Valesini G. The role of ultrasound in rheumatology. *Semin Ultrasound CT MR* 2011; 32 (2): 66-73.
18. Ruta S, Marin J, Acosta Felquer ML, et al. Utility of power Doppler ultrasound-detected synovitis for the prediction of short-term flare in psoriatic patients with arthritis in clinical remission. *J Rheumatol* 2017; 44: 1018-23.
19. Watad A, Eshed I, McGonagle D. Lessons learned from imaging on enthesitis in psoriatic arthritis. *IMAJ* 2017; 19 (11): 708-11.
20. Delle SA, Riente L. Psoriatic arthritis: what ultrasound can provide us. *Clin Exp Rheumatol* 2015; 33 (5 Suppl 93): S60-5.
21. Watad A, Eshed I, McGonagle D. Lessons learned from imaging on enthesitis in psoriatic arthritis. *IMAJ* 2017; 19 (11): 708-11.
22. Huscher D, Albrecht K, Bischoff S, et al. Patients with psoriatic arthritis and oligoarthritic subtype report higher disease burden than patients with a polyarthritic pattern—data from the German Collaborative Arthritis Centres. *Arthritis Rheumatol* 2015; 67 (suppl 10) (Abstract number: 679).
23. Ceccarelli F, Lucchetti R, Spinelli FR, et al. Early response to apremilast treatment in psoriatic arthritis: a reallife ultrasonographic follow-up study. *Rheumatology (Oxford)* 2018; 57: 1490-1.
24. Ceccarelli F, Lucchetti R, Perricone C, et al. Musculoskeletal ultrasound in monitoring response to apremilast in psoriatic arthritis patients: results from a longitudinal study. *Clin Rheumatol* 2019; 38 (11): 3145-51.