A multicentre study on high-frequency ultrasound evaluation of the skin and joints in patients with psoriatic arthritis treated with infliximab

J.J. De Agustín[1], C. Moragues[2], E. De Miguel[3], I. Möller[4], C. Acebes[5], E. Naredo[6], J. Uson[7], E. Rejón[8], L. Mayordomo[8], J. Garrido[9]

[1]Reumatology Unit, Hospital General Vall d'Hebron, Barcelona, Spain; [2]Reumatology Unit, Hospital Universitari de Bellvitge, Barcelona, Spain;[3]Reumatology Unit, Hospital La Paz, Madrid, Spain; [4]Reumatology Unit, Hospital Platón, Barcelona, Spain; [5]Reumatology Unit, Fundación Jiménez Díaz, Madrid, Spain; [6]Reumatology Unit, Hospital Severo Ochoa, Madrid, Spain; [7]Reumatology Unit, Hospital de Móstoles, Badalona, Spain;[8]Reumatology Unit, Hospital de Valme, Sevilla, Spain; [9]Social Psychology and Methodology Department, Autonomous University of Madrid, Spain.

Abstract

Objective

Our objective was to describe the ultrasound features of patients with PsA in joints and skin and their changes after treatment with infliximab.

Methods

Eight hospitals recruited PsA active patients. Clinical (joint count for pain, TJC, and swelling, SJC, pain VAS, ESR, C-reactive protein and PASI) and US variables (plaque thickness, PD signal of dermal lesions, synovitis, erosions, and PD signal, assessed by 4-category ordinal scales) were independently recorded at baseline and 4, 12 and 24-week after starting treatment with infliximab. The results were analysed with paired t-test, Wilcoxon test, ANOVA and marginal homogeneity test.

Results

Changes in 24 patients from baseline to last available data were significant for clinical variables, pain VAS, TJC and SJC as well as for ESR, CRP (all $p<0.0005$). Dermatological PASI changed from 14.6±14.9 to 2.1±4.1 and plaque thickness from 3.34±1.75 mm to 1.74±0.96 mm (both $p<0.0005$); synovitis and PD signal improved (both $p<0.0005$). Psoriatic plaque PD improved across the study ($p<0.0005$) with no signal increasing from 36.4% to 88.9% and positive PD signal decreasing from 63.6% to 11.1% of the plaques

Conclusion

Treatment with anti-TNF-α infliximab improves the symptoms of patients with PsA at joint and psoriatic skin levels from a clinical and ultrasonographic perspective.

Key words

musculoskeletal ultrasound, psoriatic arthritis, inflammation, TNF-alpha, ultrasonography

Juan José De Agustín, MD, PhD
Carmen Moragues, MD
Eugenio De Miguel, MD, PhD
Ingrid Möller, MD, PhD
Carlos Acebes, MD, PhD
Esperanza Naredo, MD
Jacqueline Uson, MD
Eduardo Rejón, MD
Lucía Mayordomo, MD
Jesús Garrido, PsyD

Please address correspondence to:
Dr Juan José De Agustín,
Hospital General Vall d'Hebron,
Unidad de Reumatología,
Passeig Vall d'Hebrón 119-129,
Barcelona 08035, Spain.
E-mail: jjagor@hotmail.com

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease of joints with a prevalence of 0.2–1% in general population, but prevalence increases to 6–42% in patients with cutaneous psoriasis (1). Both disorders are associated with important disability and a worsening of patient quality of life (2).

The physiopathology of PsA is characterised by the presence of activated T lymphocytes in the synovial tissue and in joint fluid (3, 4). Activated T cells have been implicated in psoriasis (5) and in rheumatoid arthritis (6), suggesting a common pathway in the physiopathology of both diseases. Moreover, there are similarities at histological and clinical levels. Synovitis and rheumatoid pannus, responsible for destructive bone lesions, have their equivalents in PsA, and angiogenesis increased is observed in both diseases.

The development of angiogenesis is the response to several molecular mediators, including TNF-α (tumour necrosis factor-alpha) (7), which currently is one of the most important targets in the management of PsA and other chronic inflammatory joint diseases. Moreover, inflammatory changes can be demonstrated not only at synovial level but also in the skin (8). The efficacy of anti-TNF-α drugs is due to their capacity to block the latter molecule or its soluble receptor, resulting in a reduction of neoangiogenesis.

In the last 15 years there has been dramatic progress in ultrasound applied to the study of the changes in chronic inflammatory disease of the joints, including PsA (9-13), allowing optimising the evaluation of treatment, but there are a few studies examining ultrasonographic changes in the skin and joints of PsA patients who start biological treatment (14). The goal of our pilot study is to describe the ultrasound inflammatory features of patients with PsA in joints and skin and their changes after 24-week treatment with the anti-TNF-α infliximab. To this end, Doppler technique was applied not only at joint level but also to the skin.

Materials and methods

A prospective, multicentre and blinded study in consecutive non selected PsA patients with active joint and skin involvement that start treatment with biological therapy according to the recommendations of the consensus of the Spanish Society of Rheumatology for the use of biological treatments in PsA (15). All patients started treatment with infliximab at recommended dosages of 5 mg/kg. All patients gave signed informed consent. Patients were recruited at eight Spanish Hospitals by the attendant rheumatologist who collected clinical data across the study.

Clinical assessment

Clinical and ultrasound independent evaluations were performed at week 0 (V1), baseline, and at weeks 4 (V2), 12 (V3) and 24 (V4) after starting treatment with infliximab.

At week 0, the attendant rheumatologist collected the following epidemiological data: age, sex, duration of the disease, concomitant treatments, and HLA B27 status. Clinical parameters recorded at each visit included the tender (TJC) and swollen joint counts (SJC) according to the American College of Rheumatology (ACR) score for a total of 68 and 66 joints, respectively, and the patient pain visual analog scale (pVAS) scoring the pain in the previous week among 0 to 100. Two biological parameters were also included: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In addition, the Psoriasis Area and Severity Index (PASI) was used to evaluate the degree and extent of psoriasis skin involvement at each of the clinical controls.

Ultrasound assessment

Nine ultrasonographers of the Ultrasound School of Spanish Society of Rheumatologist participated in the study. Each patient was always explored by the same ultrasonographer who was blind to all the clinical data collected by the attendant rheumatologist. The US examinations of musculoskeletal system were performed with multiplanar technique, at the clinically involved sites adopting the indications provided by the European League Against Rheumatism guidelines for musculoskeletal ultrasound in rheumatology (16, 17).

The skin ultrasound parameters were selected from consensus of the group, prior to the study. We decided the study of the plaque thickness because this is the most common grey-scale parameter studied and probably the most reproducible. In addition we considered the analysis of Power Doppler as in synovitis in order to elucidate the possibilities of this technique in the skin evaluation similar to the study of Gutierrez *et al*. (14, 18).

Ultrasonographers examined at each visit joint and skin including synovitis (S), bone structural damage (BSD), and the joint (PDJ) and skin power Doppler signal (PDS). Changes in psoriatic plaque thickness were also analysed. For each patient were selected the clinically most active joints at the time of inclusion in the study (maximum 4 joints). The two psoriatic plaques most representative for each patient were selected for skin study. Were those that diameter was between 2 and 4 cm (the large axis of the probe) and without hyperkeratosic surface in order to reduce the noise artifact. The same skin lesions were studied throughout the study, taking enough photos so that the affected area could be recognised in future examination. Thus, identification was easy even in some cases where plaques had fully recovered. Over-pigmented skin persisted on the same area in all the patients.

All centres used the Siemens Antares Premium Edition ultrasound system with a multifrequency transducer. The totalities of US evaluations were done on both longitudinal and transverse scans. The transducer was placed over the examined area directly perpendicular to the surface of skin, applying a relevant quantity of gel over it in order to provide a correct acoustic interface. All examinations were performed in both grey-scale and PD technique in order to detect the structural changes and the presence of abnormal blood flow, respectively. The basic parameters used for assessing both the joints and the skin were always the same throughout the study. Previously to the beginning of the study were decided the semiquantitative classification of the skin Doppler ultrasound evaluation in a round between the ultrasonographers. The general set of parameters for skin was: deep 2 cm, frequency 11.43 Hz (the highest), pulse repetition frequency (PRF) 0.5 MHz and the highest Power Doppler frequency 7.5 MHz, wall filters at the lowest value and colour gain fixed at the highest level not generating random noise artifacts. Particular attention was paid to pressure on the skin in order to avoid the 'blanching' of power Doppler signal due to compression by the transducer (19).

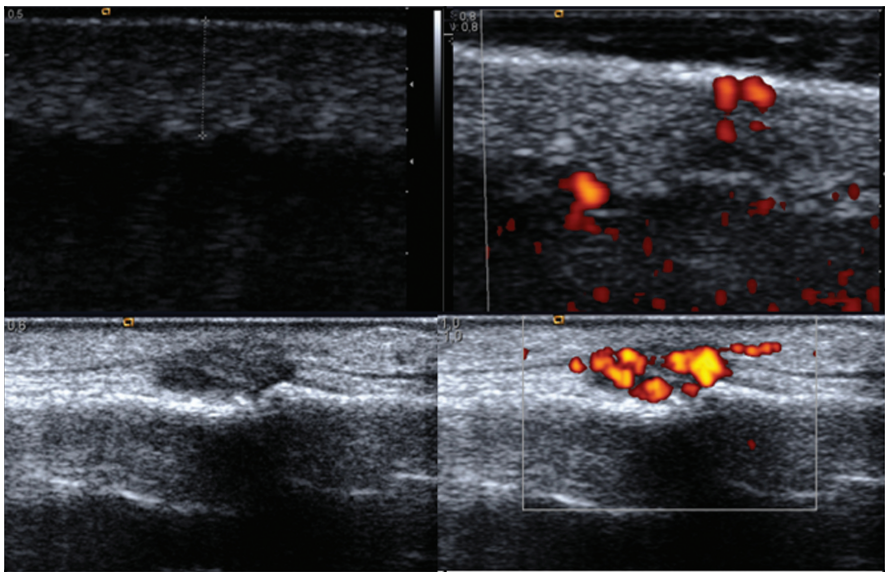

Fig. 1. Grey-scale and Power Doppler ultrasound of the psoriatic plaque and interphalangeal joint in a patient prior to begin of the treatment.

Intra-observer and inter-observer reliability were assessed on skin and joint ultrasound images recorded and pulled on a computer application which controlled exposition time and test-retest gap. Each image was evaluated two times, between 2- to 4-week apart for all the ultrasonographers. The images of the first three patients were used for this analysis.

An example of skin and joint ultrasound is shown in Figure 1.

In each patient, the same joints and skin lesions were evaluated in all visits. A four-category semiquantitative scale was developed for each ones ultrasound variables, as indicated in Table I.

Statistical analysis

Summary statistics for quantitative variables are shown as mean ± standard deviation whereas absolute frequencies and percentages are used for semiquantitative and qualitative variables. Hypothesis of no change of clinical, acute phase reactants and dermatological parameters across the study have been tested in two data sets: first, in all the patient, joints or plaques, comparing baseline values with the last available data for each patient, joint or plaque; second comparing values across the study in patient, joints or plaques with all measures across the follow-up, completers.

To compare baseline values with the last available data, *t*-test for paired samples or Wilcoxon test, depending on normality assumption, were used in quantitative variables and marginal homogeneity test, a generalised McNemar test, was used to compare distribution in severity of ultrasonographic findings. To compare mean values of clinical across the study in completers, multivariate analysis of variance for repeated measures (ANOVA) was used. In completers, marginal homogeneity test was used to compare distribution in severity of ultrasonographic findings between baseline and follow-up time points, applying Bonferroni correction since three comparisons were developed by family of data. Kappa statistics was calculated to assess intra- and inter-observer reliability.

This is the first study in which ultrasonography with power Doppler is used on psoriatic plaques. Thus, there are not

Table I. Categories of the semiquantitative scale corresponding to each ultrasound study variable.

	Synovitis	PDJ	PDS
0	Absent	No signal	No signal
1	Mild	Isolated signal	1 signal in entire psoriatic plaque
2	Moderate	Confluent signals in <50% of synovial	1–3 signals in entire psoriatic plaque
3	Severe	Confluent signals in >50% of synovial	>3 signals in entire psoriatic plaque

Table II. Demographic, clinical and acute phase reactants at baseline.

	Mean	(SD)	Frequency	(%)
Demographics				
Sex (male)			12	(50.0)
Age (years)	45.2	(14.4)		
Age at disease onset (years)	37.3	(13.5)		
Clinical				
Pain (0 – 100 VAS, patient)	68.63	(14.76)		
PJC (68 joints)	11.88	(8.89)		
SJC (66 joints)	4.77	(3.25)		
MS	65.43	(48.83)		
Acute phase reactants				
ESR (mm/H)	39.36	(25.20)		
CRP (mg/dl)	18.72	(24.03)		
Dermatological				
PASI	14.60	(14.92)		
Plaque thickness (mm)	3.34	(1.65)		

PJC. painful joint counts; SJC: swollen joint counts; MS: morning stiffness; PASI: psoriasis area and severity index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

prior data to base sample sise calculation. Sample size of this pilot study was established in 24 patients in order to obtain result in a short-term more than testing specific hypothesis. Thus, imputation procedures were not used to substitute missing data during follow-up.

P-values ≤0.05 were considered as significant, exception made of Bonferroni correction application where $p \leq 0.017$ was considered as significant. All analyses were developed with the statistical package SPSS 15.0.

Results

Twenty-four PsA patients were recruited in 8 centres. All 24 patients underwent the initial (week 0, baseline) visit as well as visit V2 (week 4); in turn, 23 patients completed visit V3 (week 12), one subject being withdrawn from the study because of infection, and 19 completed visit V4 (week 24), four subjects being lost to follow-up.

Demographic and clinical characteristics of sample are shown in Table II.

At baseline, a total of 56 joints from 24 patients were symptomatic and selected to be explored: 14 carpal, 2 elbow, 2 shoulder, 7 proximal interphalangeal finger, 13 metacarpophalangeal, 7 metatarsophalangeal, 9 knee, and 2 ankle joints. All 56 joints presented some degree of synovitis in grey-scale, 43/56 (78%) showed bone cortical alterations, and 41/56 (73%) presented some degree of increased Doppler signal. Moreover, 33 psoriatic plaques from 24 patients were explored: 14 on the lower extremities, 8 on the upper extremities, and 11 on the trunk. The mean plaque thickness was 3.34±1.65 mm. At baseline, 21/33 (64%) presented some degree of increased Doppler signal.

At week 4, 56 joints and 33 plaques were studied. Clinical improvement meant eliminating some medication in 6 patients (2 DMARDs, 1 corticoid, 3 NSAIDs).

At week 12, 52 joints and 29 psoriatic plaques were explored. Clinical improvement allowed dose reduction of DMARD, NSAID and corticoids in 1, 3 and 2 patients respectively. Methotrexate was added to 2 patients due to inefficacy. One patient withdrew the study at week 12 due to severe infection.

At the last visit, 24 weeks, four more patients were missing due to loss to follow-up. 44 joints and 27 psoriatic plaques were explored. Clinical improvements allowed removing DMARD in one patient and reducing NSAID in other. On the contrary, biological therapy was removed in two patients due to pericarditis tuberculoses and tooth infection respectively, and ibuprofen was introduced in one patient due to a metatarsophalangeal inflammatory episode.

Summary descriptive statistics of clinical, acute phase reactants and dermatological evolution across the study are shown in Table III. Mean changes from baseline to last available data were statistically significant for clinical variables, pain VAS (from 68.6±14.8 to 24.2±23.4 [$p<0.0005$]), TJC (from 11.9±8.9 to 3.3±4.1 [$p<0.0005$]) and SJC (from 4.8±3.3 to 1.6±1.9 [$p<0.0005$]), as well as for MS (from 65.4±48.8 to 14.8±21.3 [$p<0.0005$]). Mean changes from baseline to last available data were also statistically significant for acute phase reactants, ESR (from 39.4±25.2 to 15.6±12.1 [$p<0.0005$]) and CRP (from 18.5±24.6 to 3.9±3.9 [$p<0.0005$]). as well as for dermatological. PASI (from 14.6±14.9 to 2.1±4.1 [$p<0.0005$]) and plaque thickness (from 3.34±1.65 to 1.74±0.96 [$p<0.0005$]). Analyses of completers by multivariate ANOVA of repeated measures show a significant reduction of mean pain ($p<0.0005$), PJC ($p=0.002$), SJC ($p=0.002$), RM ($p=0.014$), ESR ($p=0.010$), PASI ($p<0.0005$) and plaque thickness ($p=0.014$) across the follow-up period. Reduction in CRP was not statistically significant ($p=0.082$). The pattern of change (Fig. 2) was an acute reduction between baseline and week 4 followed by a plateau or smaller additional reductions.

Summary descriptive statistics of ultrasonographic evolution across the study are shown in Table IV, showing improvement of synovitis and power Doppler signal at level of joints and plaques

Table III. Statistics summary of clinical, acute phase reactants and dermatological evolution across the study.

	Baseline			Week 4			Week 12			Week 24		
	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
Pain	24	68.6	(14.8)	23	35.5	(22.1)	23	25.0	(19.9)	19	22.1	(22.5)
TJC	24	11.9	(8.9)	23	4.7	(6.0)	23	3.7	(5.5)	19	3.3	(4.6)
SJC	24	4.8	(3.3)	23	2.4	(2.7)	23	1.2	(1.9)	19	1.5	(2.0)
MS	24	65.4	(48.8)	23	17.4	(19.2)	23	9.4	(12.0)	19	10.3	(22.9)
ESR	24	39.4	(25.2)	23	17.0	(12.2)	23	13.8	(10.7)	19	15.4	(13.4)
CRP	24	18.7	(24.0)	23	4.4	(5.2)	23	4.1	(4.8)	19	3.0	(2.5)
PASI	24	14.6	(14.9)	23	4.2	(4.7)	23	1.5	(1.6)	19	0.9	(1.2)
PThick	31	3.34	(1.65)	30	2.18	(0.60)	29	1.83	(0.71)	27	1.78	(1.01)

TJC. tender joint counts; SJC: swollen joint counts; MS: morning stiffness; PASI: psoriasis area and severity index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PThick: plaque thickness.

across the study. It is remarkable that whereas at baseline all joints showed synovitis mild to severe, 24 weeks later 26 joints (59.1%) did not show synovitis at all, and severe synovitis was not detected at any joint. The percentage of joints without synovitis increased across the study from 0.0% (baseline) to 32.1% (week 4), 46.2% (week 12) and 59.1% (week 24). Concerning power Doppler, 26 joints (46.4%) showed confluent signals at baseline, whereas 24 weeks later only 3 joints (6.8%) showed confluent signals always in <50% of synovial. The percentage of joints without PDJ signal increased across the study from 26.8% (baseline) to 67.9% (week 4), 75.0% (week 12) and 70.5% (week 24). At level of psoriatic plaque, 21 plaques (63.6%) showed 1 or more signals at baseline, whereas 24 weeks later only 3 plaques (11.1%) showed 1 or more signals. The percentage of plaques without PDS signal increased across the study from 36.4% (baseline) to 90.9% (week 4), 89.7% (week 12) and 88.9% (week 24). Changes in severity of ultrasonographic findings from baseline to last available data were tested with marginal homogeneity test. Statistically significant changes were found in synovitis (p<0.0005), power Doppler joint (p<0.0005) and power Doppler plaque (p<0.0005). Changes in severity of BSD were not significant (p=0.162). When considering only plaques with ultrasonographic measures in all visits, marginal homogeneity test offered the same results: statistically significant changes were found in synovitis (p<0.0005), power Doppler joint (p<0.0005) and power Doppler plaque (p<0.0005) and changes in severity of bone structural damage were not significant (p=0.201). Significant changes in severity of ultrasonographic findings for completers were significant since the week 4.

Intra- and inter-observer reliability

The analysis of scores assigned to recorded images of joints and plaques by sonographers yielded a global intra-observer kappa coefficient of 0.617, and a global inter-observer kappa coefficient of 0.333. According to the classification of Landis and Koch (1977) (20), these coefficients are considered to be substantial and discrete, respectively.

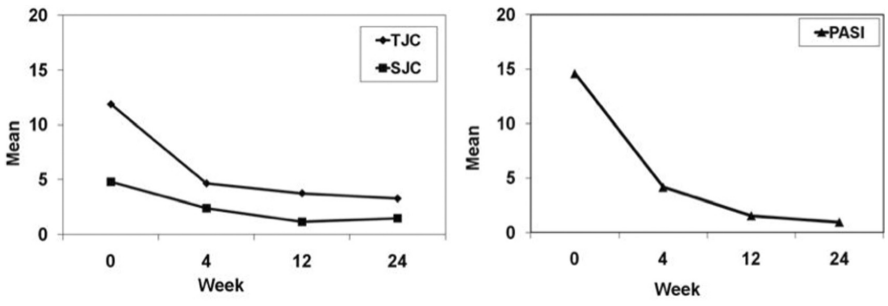

Fig. 2. Changes in clinical, tender joint counts (TJC) and swollen joint counts (SJC) (left panel) and psoriasis area severity index (PASI) (right panel), across the study.

Discussion

Pharmacological treatment with infliximab during 6 months improves clinical and biological markers in patients with psoriatic arthritis (PsA). Decreases in painful (TJC) and swollen joint counts (SJC) were clinically relevant, exceeding 50% after 24 weeks. Changes in TJC and SJC appeared early (within 4 weeks (Fig. 2), and persisted during the 6 months of the study, as reported in similar studies with anti-TNF-α drugs (23-26).

Regarding the ultrasound findings, early and significant improvements were recorded in synovitis and joint pulsed Doppler signal (PDJ) which were extended for the full course of the study. At the end of follow-up, synovitis and PDJ had disappeared entirely in most of the joints examined (26 and 31 joints, respectively). Our findings agree with those reported by Naredo *et al*. (21) at joint level on rheumatoid arthritis and PsA treated with adalimumab, using ultrasound as study endpoint. Moreover, an early and extended reduction in knee synovitis has been reported in patients with PsA and rheumatoid arthritis under treatment with etanercept (22). Gutierrez *et al*. have reported similar results in an etanercept group of psoriatic patients using power Doppler technique (14)

Concerning the psoriatic plaques, a reduction in thickness and Doppler signal was detected from qualitative and quantitative perspectives: after 6 months the mean plaque thickness was 1.78 mm *versus* 3.34 mm at baseline, and no Doppler signal was recorded in 24 of the 27 plaques. We consider these

Table IV. Summary statistics of ultrasonographic evolution of joints and psoriatic plaques across the study.

	Baseline		Week 4		Week 12		Week 24	
	n	%	n	%	n	%	n	%
Synovitis (S)								
Absent	0	(0.0)	18	(32.1)	24	(46.2)	26	(59.1)
Mild	15	(26.8)	25	(44.6)	23	(44.2)	13	(29.5)
Moderate	30	(53.6)	13	(23.2)	5	(9.6)	5	(11.4)
Severe	11	(19.6)	0	(0.0)	0	(0.0)	0	(0.0)
Total	56	(100.0)	56	(100.0)	52	(100.0)	44	(100.0)
Power Doppler joint (PDJ)								
No signal	15	(26.8)	38	(67.9)	39	(75.0)	31	(70.5)
Isolated signal	15	(26.8)	10	(17.9)	9	(17.3)	10	(22.7)
Confluent signals in <50% of synovial	16	(28.6)	7	(12.5)	4	(7.7)	3	(6.8)
Confluent signals in >50% of synovial	10	(17.9)	1	(1.8)	0	(0.0)	0	(0.0)
Total	56	(100.0)	56	(100.0)	52	(100.0)	44	(100.0)
Power Doppler psoriatic plaque (PDS)								
No signal	12	(36.4)	30	(90.9)	26	(89.7)	24	(88.9)
1 signal in entire psoriatic plaque	11	(33.3)	2	(6.1)	2	(6.9)	2	(7.4)
1-3 signals in entire psoriatic plaque	9	(27.3)	1	(3.0)	1	(3.4)	1	(3.7)
>3 signals in entire psoriatic plaque	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)
Total	33	(100.0)	33	(100.0)	29	(100.0)	27	(100.0)

changes to be very important, pointing out the treatment usefulness in controlling the dermatological symptoms of psoriasis. Our study is the longest to report a reduction in skin inflammatory lesions as assessed by ultrasound, in PsA patients with biological treatment. Up to date, skin ultrasound evaluation in PsA has been constrained to analysis changes in psoriatic plaque thickness using very high-frequency transducers, above 20 MHz (up to 100 MHz) (29-33). Now, we have high-frequency transducers that allow us to study both the joints and the skin, with high sensitivity in showing up inflammatory changes. Furthermore, using additionally the Doppler technique as Italian group (14, 23), we are able to identify the characteristic changes in vascularisation of PsA also at skin level. Doppler technique allows us to detect significant changes in cutaneous vascularisation of the inflamed plaques, which are coincident with the reduction in angiogenesis at both skin and synovial level reported in patients under biological therapy (24, 25) and the reduction of factor VIII staining and VEGF staining (14). Accordingly, Goedkoop *et al*. (26) recorded a significant reduction in the number of vessels at dermis and synovial level four weeks after starting treatment with infliximab. Moreover, some earlier studies reported psoriatic plaque improvement with both infliximab and etanercept (24, 25). As in our results, in these reports the cutaneous changes were manifested early, and persisted throughout follow-up.

The role of ultrasound in evaluating psoriatic lesions has being established, and more validation studies are needed particularly at skin level. Although it is possible to accuracy measure the thickness of the plaque and even identify different parts of the latter, to date no evaluations had been made of whether changes can be demonstrated as a result of administration of some of the drugs used to treat this chronic inflammatory joint disease. Both, Gutierrez and our study, offers new evidence of the usefulness of the technique in application to follow-up, and for evidencing the changes that appear with biological therapy and in our opinion can help to define the role of ultrasound in this disease. However, there are some limitations to our study, such as the limited sample size involved (24 patients) is small due to this is a pilot study, designed to assess the utility of the skin study in PsA using ultrasonography tools, including Power-Doppler. This fact is probably one of the reasons why it has not been possible to observe a correlation between ultrasonography and clinical variables. But there are also other factors which may explain why no correlation could be established between the ultrasound parameters and the clinical variables. One of them and probably the most relevant is that ultrasonography is more sensitive image tool than physical examination in the assessment of synovitis. Therefore, with ultrasonography, we can demonstrate subclinical synovitis improving clinical assessment (27, 28) and also to assess activity remission of joint disease (28). Other authors have demonstrated similar conclusions and they have joined bad correlations between clinical and ultrasonographic observations (29-33).

We have demonstrated significant changes in each one of clinical and ultrasonographic variables. Additionally we have provided data about the utility of this tool concerning a specific ultrasonographic machine for the skin study in PA. The frequency of grey-scale 11.43 and power Doppler 7.5 mHz is the maximum achievable frequency for this type of machine, and the settings were sensitive enough to recognise well thickness and vascularisation of the epidermis and dermis in these patients. We believe this type of machine allows for the study of skin lesions in patients under biological treatment. Probably with a higher frequency we would have seen better the thickness and Doppler signal, but the observe results support our decision to use this ultrasound machine. It would therefore be advisable to confirm our observations with a larger series of patients. It also would be interesting to determine whether these changes persist for periods of time beyond the 6 months considered in our study.

Global intra-observer kappa coefficient of 0.617 and inter-observer kappa of 0.333 were obtained for the entire ultrasonographers group. According to Landis and Koch (1977) (20), these coefficients are considered substantial and discrete, respectively. It is well known that inter-observer Kappa coefficient is not as good as in other studies (34-36). Sometimes it is difficult to compare results from a large group of ultrasonographers, as in our case, even when they are equally experienced.

Intra-observer coefficient was not the highest achievable, but it was judged sufficient for the purpose of the study. These coefficients present one of the limitations of this study.

In our study and in other publications, the efficacy of anti-TNF-α therapy (infliximab) in controlling the symptoms of patients with PsA has been demonstrated. In addition, we have shown that treatment response of both the joint and psoriatic skin lesions are rapid from the clinical and ultrasound perspectives.

Lastly, new evidence would be required to determine whether there is a correlation among the severity of psoriatic plaque inflammation, the inflammatory joint lesion, and the secondary structural damage. Our efforts should be directed to clarify whether ultrasound can play a relevant role in this field, since a simple ultrasound evaluation of the skin could possibly provide clues to the prognosis of many patients. This in turn would be of great importance for the taking of treatment decisions in this disease.

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