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Original article

Power Doppler ultrasound monitoring of response to anti-tumour necrosis factor alpha treatment in patients with rheumatoid arthritis

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Abstract

Objectives. To monitor by power Doppler US (PDUS) the short-term response to anti-TNFα therapy in six target joints of RA patients; to correlate PDUS findings with clinical assessments and laboratory indices of disease activity.

Methods. Consecutive RA patients starting anti-TNFα therapy were included and studied at baseline and 3 months later. Clinical (number of tender joints; number of swollen joints; Visual Analogue Scale; DAS28) and laboratory (ESR and CRP) assessments were performed. All patients were evaluated by PDUS at six target joints (II MCP, wrist, knee bilaterally). The components of synovitis (synovial hypertrophy, joint effusion, and power Doppler) were analysed and graded (0–3 semi-quantitative score). Moreover, by summing the PDUS findings, three different scores were calculated: a single inflammatory lesion score (0–18, for synovial hypertrophy, effusion, power Doppler), a joint score (0–18; at II MCP, wrist and knee joints) and a global score (0–54; sum of all abnormalities).

Results. Sixty-eight RA patients were studied. A significant decrease in the joint score in all articular sites (MCP, $P = 0.003$; knee, $P = 0.002$; wrist, $P = 0.0001$) as well as in the scores of the single components of synovitis ($P = 0.0001$–0.002) and in the global 6-joint score ($P = 0.0001$) was found. All clinical and laboratory parameters were significantly decreased at follow-up ($P = 0.0001$–0.001). A moderate significant positive correlation was observed between the global PDUS score and DAS28 ($r = 0.38$; $P = 0.001$).

Conclusion. PDUS is a sensitive-to-change imaging modality for monitoring the short-term response to anti-TNFα treatment in RA patients. The assessment of a limited number of joints makes the evaluation feasible in rheumatology practice as a complementary tool to clinical assessment.

Key words: rheumatoid arthritis, synovitis, scoring systems, power Doppler ultrasound, follow-up.

CLINICAL SCIENCE

Rheumatology key messages

- Power Doppler US is a sensitive-to-change imaging modality for monitoring the short-term response to anti-TNFα treatment in RA patients.
- Use of a feasible sonographic joint count facilitates the application of power Doppler US in daily rheumatology practice.

Introduction

RA is a chronic inflammatory disease characterized by symmetrical polyarticular involvement. Synovitis is the main feature of the inflammatory process [1]. In recent years, the mechanisms underlying the beginning and the persistence of the inflammation are becoming clearer, due to the possibility of observing and understanding the

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cellular subsets and the molecular pattern of cytokines involved in the process [2–6]. Among them, TNFα has been shown to be fundamental in the pathogenesis of RA, triggering and maintaining the intra-articular inflammation. It mediates the release of other pro-inflammatory cytokines (IL1, IL6, IL23), the control of the migration of leucocytes to sites of inflammation, the upregulation of the expression of the endothelial adhesion molecules, the increase in synovial and fibroblastic proliferation, the progression of the intra-articular damage (cartilage destruction and bone resorption), the neovascularization of the synovial tissue, the activation of the acute-phase response, and the production of PGE2, which is responsible for the possible systemic involvement of the pathology [3, 6–8]. Consequently, with the major role of TNFα in RA, anti-TNFα agents represent a revolution in the treatment of the disease, changing the target of therapy from improvement to remission [9–11]. Therefore, new ways to define disease activity are required, it being well documented that lack of symptoms does not necessarily reflect a lack of joint inflammation; in the case of subclinical synovitis, the possibility of progression of articular damage is still present [12, 13]. In this scenario, power Doppler US (PDUS) assumes a relevant role in the evaluation of joint inflammation. The potential for it to be used in real time, to estimate both structural damage and inflammatory alterations, along with other advantages such as the absence of invasiveness and good patient compliance, make PDUS a very useful technique for monitoring articular disease activity and the response to anti-TNFα treatment [14–16]. Grey scale (GS) US assessment in RA enables visualization of joint and peri-articular alterations, such as synovial hypertrophy, synovial effusion, tenosynovitis, bursitis, cartilage abnormalities and bone erosions. The PDUS technique allows the observation of pathological synovial vascularization that is related to active inflammation [14, 17]. This finding thus provides the opportunity to differentiate between active and inactive synovitis, a differentiation that may influence the therapeutic approach to achieving remission, if disease is still active, and which may improve the outcome for the patient [17, 18]. The intra-articular PDUS signal has a strong correlation with the radiological progression of the pathology, even in patients who have reached clinical remission, and it is associated with flares [19–21]. Therefore, ultrasonographic assessment in RA can be considered as complementary to clinical evaluation when seeking to define the most appropriate therapeutic decision for the patient. However, polyarticular US assessment is time consuming and not feasible in daily clinical rheumatology practice, and it is therefore fundamental to identify target joints in RA, for which assessment could be representative of global disease activity. The 6-joint score previously demonstrated validity, sensitivity to change and feasibility for the assessment and monitoring of inflammation in patients with RA [16]. The objectives of the present study were to use PDUS to monitor the short-term response to anti-TNFα therapy in six target joints of RA patients and to correlate PDUS findings with clinical and laboratory indices of disease activity.

Patients and methods

A total of 68 consecutive patients, who fulfilled the 2010 RA classification criteria [22] were recruited in the Rheumatology Unit of the Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma. All the patients started therapy with an anti-TNFα agent in association with MTX or other DMARD. Of these, 43 had already been under glucocorticoid treatment for at least 6 months. Anti-TNFα agents were administered according to the Italian Consensus on the use of biologic drugs for this treatment. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Comitato Etico Sapienza Università di Roma). Informed consent was obtained from all patients enrolled.

Clinical and laboratory evaluation

Clinical evaluation was performed by a single rheumatologist, blinded to the results of the US assessment that had been carried out on the same day. Swollen joint count on 28 joints (SJC28), tender joint count on 28 joints (TJC28), patient visual analogue scale for disease activity (VAS-patient, 0–100 mm), physician visual analogue scale for disease activity (VAS-physician, 0–100 mm) and DAS on 28 joints (DAS28) were registered for each patient on an electronic database.

Each subject underwent peripheral blood sample collection. ESR (mm/h; normal $<$20 mm/h; Westergren method) and CRP (mg/dl; normal range $<$10 mg/l) were determined via laboratory tests. Each parameter was evaluated at baseline and after 3 months.

US evaluation

A single rheumatologist, experienced in musculoskeletal US, who was blinded to the clinical and laboratory data, performed the PDUS examination at baseline and at 3 months follow-up. An assessment of six joints (II MCP, wrist and knee, bilaterally) was performed, with a multiplanar GS and PD examination, using a MyLab 70 XVision Gold machine (Esaote, Genova, Italy) with a multifrequency linear array transducer (6–18 MHz; 13 MHz for the knee, 15 MHz for the wrist and 18 MHz for II MCP). Settings for PD were: frequency 9.1 MHz, pulse repetition frequency 750 Hz, PDUS gain 50%, low filters. The US assessment and scanning technique included evaluation of the synovial sites in six target joints (wrist—radiocarpal, midcarpal, ulno-carpal joints; second MCP—dorsal side, palmar side; knee—suprapatellar recess, lateral parapatellar recess) as previously reported [16]. These joints and synovial sites were selected according to the previous study on the 6-joint score by Perricone *et al*. [16]. According to the OMERACT definitions [23], in each joint, the presence of synovial effusion (SE) and synovial hypertrophy (SH) and intra-articular PD signal were registered as follows: SE as an abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible, but does not exhibit PD signal; SH as an abnormal hypoechoic intra-articular tissue that is

non-displaceable and poorly compressible and may exhibit PD signal. The single components of synovitis (SE, SH, PD) were graded according to a 0–3 semi-quantitative score depending on their severity [SE and SH: 0 = absent, 1 = mild, 2 = moderate, 3 = marked; PD signal: 0 = absent (no synovial flow), 1 = mild (⩽3 PD signals), 2 = moderate (>3 PD signals in <50% of the synovial area) and 3 = marked (>3 PD signals in >50% of the synovial area)] [16].

Summing the scores for the elementary lesions in each joint differently, we calculated: a score for the single abnormalities in all six joints (the sum of the scores for each one of the elementary lesions in all six joints: US-SE score, US-SH score; US-PD score, range 0–18); a score for the single joint bilaterally (summing the basic lesions for each joint; score of the II MCP joint: US-II MCP, score of the wrist: US-Wrist, score of the knee US-Knee, range 0–18); a global score at patient level (summing all registered alterations at all joint sites, range 0–54). An increase in the various scores during the follow-up was considered to be a worsening of the pathological process, and a decrease was considered an improvement.

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 13.0 (SPSS, Chicago, IL, USA). Quantitative variables (DAS-28, US parameters) were given as the mean (SD) and range. Comparisons between groups were performed using contingency tables and Pearson's test. Comparisons between parametric variables were performed with the Wilcoxon's test. Pearson's and Spearman's tests were used to perform the correlation analysis. Sensitivity to change of the US variables was tested by comparing the mean change in US assessment from baseline to 3 months; in addition, we evaluated the correlation between the changes in US assessment and the variations in DAS-28 from baseline to 3 months (Spearman's test). Values for P of < 0.05 were considered statistically significant.

Results

Sixty-eight consecutive patients [11 men and 57 women, mean age 53 (15.16) years, mean duration of disease 143.6 (41 months)] were included in the study. The main demographic, clinical and laboratory parameters of the enrolled population are reported in Table 1.

All the patients started therapy with an anti-TNFα agent (45 patients: etanercept 50 mg s.c. weekly; 23 patients: adalimumab 40 mg s.c. every 2 weeks) in association with MTX or other DMARDs (52 patients; SSZ, HCQ, LEF, CSA). Forty-three patients started co-treatment with glucocorticoids. A significant decrease in clinical and laboratory parameters was registered after 3 months of treatment with respect to baseline (Table 2).

Particularly, DAS28 decreased from a mean value of 5.2 at basal time, to a mean value of 3.9 at 3 months ($P = 0.0001$); SJC28 decreased from 7.1 to 3.4 ($P = 0,0001$); TJC28 decreased from 9.1 to 5.2 at 3 months ($P = 0.0001$); patient VAS score was reduced from a mean of 58.2 to a mean of 36.5 ($P = 0.0001$); physician VAS score had a decrease from 52.3 to 33.8 ($P = 0.0009$); ESR mean value decreased from 29 to 21.2 mm/h ($P = 0.001$); CRP decreased from 14.9 to 8.7 mg/l ($P = 0.001$).

Table 1 Demographic, clinical and laboratory data of 68 patients at the beginning of therapy with anti-TNFα

Parameter	*n* = 68
Demographic parameters	
Age, mean (SD), years	53.0 (15.16)
Duration of disease, mean (S.D.), months	143.6 (41)
M/F	11/57
Laboratory parameters	
ESR mean (S.D.), mm/h	29 (21.6)
CRP, mean (S.D.), mg/l	15 (17.3)
Disease activity	
VAS physician, mean (S.D.)	52.3 (22.1)
No. of swollen joints, mean (S.D.)	7.1 (6.6)
No. of tender joints, mean (S.D.)	9.1 (7.7)
VAS patient, mean (S.D.)	58.2 (24.9)
DAS28, mean (S.D.)	5.2 (1.3)
Therapy	
Corticosteroids, *n* (%)	43 (63.2)
Anti-TNFα	
Etanercept, *n* (%)	45 (66.2)
Adalimumab, *n* (%)	23 (33.8)
DMARDs, *n* (%)	52 (76.4)
MTX	41 (60.3)
SSZ	8 (11.7)
HCQ	7 (10.3)
LEF	7 (10.3)
CSA	2 (2.9)
Anti-TNFα monotherapy, *n* (%)	7 (10.3)

VAS: visual analogue scale.

After 3 months of therapy, a significant reduction in all three PDUS-analysed scores was registered. Results of the US assessment are reported in Table 3. Particularly, in terms of single components of synovitis, the mean score significantly decreased for SE from 5.2 at baseline to 3.5 at the 3-month follow-up ($P = 0.0001$); for SH from 5.3 to 3.2 ($P = 0.0001$); and for PD from 3 to 1.6 ($P = 0.002$).

Considering the US joint score, a reduction was registered at the II MCP (from 2.7 to 1.2; $P = 0.003$), wrist (from 7 to 4.4; $P = 0.0001$) and knee (from 4.1 to 2.7; $P = 0.0001$) joint levels. Fig. 1 shows the presence of synovitis at the level of the knee joint at baseline and no evidence of it at follow-up. At patient level, the global US score decreased from a basal mean value of 13.9 to a follow-up mean value of 8.4 ($P = 0.0001$).

Results emerging from the US evaluation were in substantial agreement with clinical and serological evaluation. A significant reduction in DAS28, SJC28, TJC28, patient VAS for disease activity, and physician VAS for disease activity was observed after 3 months of treatment. Finally, a significant correlation between the global PDUS score

Table 2 Clinical and laboratory data of the 68 patients at the beginning and after 3 months of therapy

Parameter	Basal ($n = 68$)	3 months ($n = 68$)	*P*-value
ESR, mean (S.D.), mm/h	29 (21.6)	21.2 (18.6)	0.001
CRP, mean (S.D.), mg/l	14.9 (17.3)	8.7 (10)	0.001
Number of swollen joints, mean (S.D.)	7.1 (6.6)	3.4 (4.8)	0.0001
Number of tender joints, mean (S.D.)	9.1 (7.7)	5.2 (6.5)	0.0001
VAS patient, mean (S.D.)	58.2 (24.9)	36.5 (28.7)	0.0001
VAS physician, mean (S.D.)	52.3 (22.1)	33.8 (23.0)	0.0001
DAS28, mean (S.D.)	5.2 (1.3)	3.9 (1.5)	0.0001

VAS: visual analogue scale.

Table 3 Ultrasonographic data of the 68 patients at the beginning and after 3 months of therapy

Parameter	Basal ($n = 68$)	3 months ($n = 68$)	*P*-value
US-SE, mean (S.D.) (range 0–18)	5.2 (3.6)	3.5 (2.4)	0.0001
US-SH, mean (S.D.) (range 0–18)	5.3 (3.7)	3.2 (2.5)	0.0001
US-PD, mean (S.D.) (range 0–18)	3 (3.6)	1.6 (1.8)	0.002
US-II MCP mean (S.D.) (range 0–18)	2.7 (3.9)	1.2 (1.9)	0.003
US-Wrist, mean (S.D.) (range 0–18)	7.0 (5.0)	4.4 (3.2)	0.0001
US-Knee, mean (S.D.) (range 0–18)	4.1 (4.3)	2.7 (3.1)	0.002
Global US score, mean (S.D.) (range 0–54)	13.9 (10.4)	8.4 (6.1)	0.0001

US-SE: ultrasound-synovial effusion; US-SH: ultrasound–synovial hypertrophy; US-PD: US-power Doppler.

and DAS28 at the 3-month follow-up ($R = 0.38$, $P = 0.0016$) was found.

Discussion

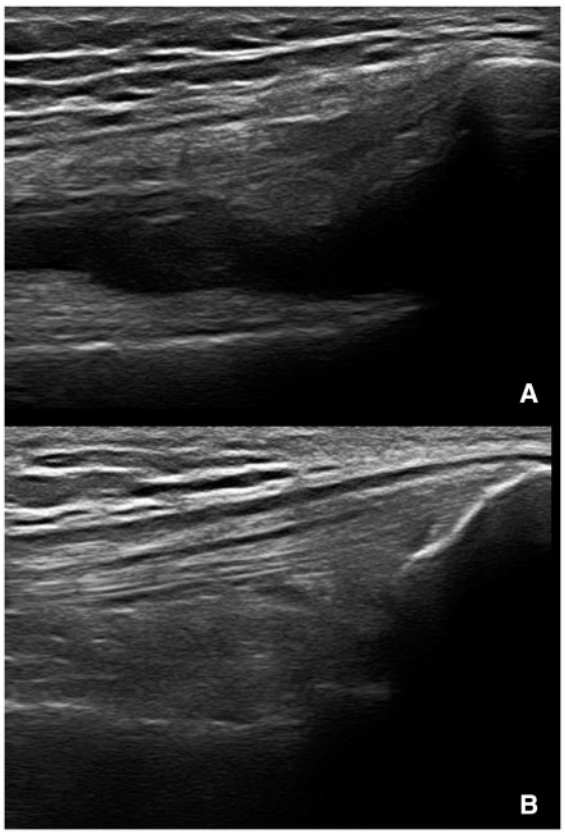
The present US study, conducted in patients affected by RA and focused on the evaluation of synovial inflammatory alterations (SE, SH and PD signal) in six target joints, demonstrated a significant decrease in PDUS parameters considered as indices of the efficacy of anti-TNFα treatment at the 3-month follow-up. Our results demonstrate that PDUS in six target joints is a useful and feasible technique for monitoring patients with RA in treatment with anti-TNFα agents, in relation to its ability to detect synovial inflammatory abnormalities in real time. The significant parallel reduction in all clinical and laboratory parameters, and the correlation between the global PDUS score and DAS28 at the 3-month follow-up, confirm these aspects.

In the last few decades, the use of musculoskeletal US as a valid, reliable and sensitive-to-change method for the evaluation and monitoring of disease activity in RA has been frequently reported [15, 24–28]. Thanks to technological improvement in US equipment and the use of internationally approved scanning techniques and definitions for normal findings and pathology, both GS and PD assessments are widely used in the assessment of inflammatory and structural lesions, and in disease follow-up in relation to early disease. Currently, PDUS represents a complementary tool for the clinical evaluation of the RA patient and it plays a role in the determination of joint inflammatory state and structural damage progression, in addition to the serological and radiological methods [17, 18, 29–32].

Over the past few decades, a large number of studies evaluating the efficacy of anti-TNFα treatment and the sensitivity of musculoskeletal US in monitoring the response at joint level have been conducted. Hau *et al*. [33] in 2002 published the first US study on the efficacy of etanercept in five RA patients, evaluating the reduction of local synovial vascularization at the level of the II MCP joints. After that, various studies analysed the role of US in determining the response to anti-TNFα treatment [22, 34, 35] after various intervals of follow-up, highlighting the correlations between US findings and clinical and laboratory parameters.

Even if the sensitivity to change of PDUS is well documented, a fundamental point has yet to be established: which and how many joints have to be assessed in the evaluation of RA patients' responsiveness? At the moment, there is a lack of consensus, and in this context, the present study represents a further application of Perricone *et al*.'s work [16], in which we demonstrated the sensitivity to change and feasibility of US assessment at the level of six target joints. Because of the typical polyarticular involvement in RA patients, in clinical rheumatology practice it is fundamental to obtain a correct balance between an extended sonographic evaluation (at the level of the involved joints) and a reduced assessment (at the level of target joints) that proves to be feasible and easily applied at the bedside. A feasible

Fig. 1 US of the knee joint in a RA patient



Anterior longitudinal scan at the level of the suprapatellar recess. (**A**) Synovial hypertrophy and joint effusion are detected at baseline. (**B**) No evidence of synovitis is present at follow-up.

US assessment has to be quick to perform and easy to apply in clinical practice, but it also has to be sensitive to change. For this purpose, the selection of target joints that represent the global disease activity is important. The 6-joint assessment has these characteristics, and, in addition, it offers symmetrical evaluation in a disease that has a typically bilateral involvement. In 2012, we developed a reduced 6-joint US model after a process of data reduction on the basis of Naredo *et al.*'s 2008 work [36]. We first conducted a 12-joint assessment and, after analysing the data statistically, significant correlation was found between the extended evaluation and the 6-joint assessment.

A number of earlier studies led to the development of innovative reduced US scores. Particularly, Naredo *et al*. [36] in 2008 evaluated the sensitivity to change of a 12-joint assessment (wrist, II MCP, III MCP, knee, ankle and elbow joints bilaterally) in RA patients under biologic treatment, obtained by a process of data reduction from US evaluation of the 44 joints included in the DAS44 index. In 2009, Backhaus *et al.* [37] proposed a reduced assessment, the seven US score, evaluating RA synovitis elementary lesions in the follow-up of anti-TNFα + MTX and glucocorticoids therapy. The joints assessed were: II and III MCP, II and III PIP, II and V MTF, considering only the clinically dominant side of the body. In 2010, Hammer *et al*. [38] proposed an extended assessment of 78 joints in RA patients in adalimumab therapy; however, this system proved to be time consuming and not feasible, although it had a high sensitivity to change.

Hammer *et al*. in 2011 [39] compared 7- and 12-joint assessments with 78-joint evaluation in a cohort of 20 patients affected by RA under adalimumab treatment during a 12-month follow-up period, showing evidence of a strong correlation between the reduced and the comprehensive evaluation, with the advantage of feasibility in the former. In a systematic review in 2011, Mandl *et al*. [40] analysed the literature with respect to the US joint count and scoring systems for assessment of synovitis in RA. In order to evaluate the responsiveness and applicability of reduced joint assessment, the data from the 7-joint score [38] and 12-joint score [36] were taken into consideration. Based on the data from Naredo's study, the 7-joint score was applied and it demonstrated good responsiveness with the new dataset. Both types of reduced joint count were sensitive to change and feasible, although the application of the 7-joint count bilaterally (14 instead of 7 joints) was characterized by a higher sensitivity to change [40]. In 2011, the OMERACT task force reported data on responsiveness in RA [41]. They introduced the US-GLOSS (US GLObal Synovitis Score), a combined score (GS + PD) at patient level, assessing 22 paired joints. The US-GLOSS was compared with 7- and 12-joint assessments and all measures were revealed to have a similar sensitivity to change; from the OMERACT 11 US Workshop, the need emerged for further study of reduced assessmentsin order to reach consensus on the number of joints to include [41]. In this context, the reduced 6-joint count represents a novel joint count that has increased the possibility of use of PDUS in daily rheumatology practice assessment of response to treatment. To define the real status of joint inflammation, in addition to clinical evaluation the importance of including a US assessment has recently been underlined, particularly PD activity [42, 43]. This aspect may have relevant consequences for the therapeutic choices required to achieve real efficacy of treatment [19, 20, 42, 44].

Some limitations in our study should be noted. The use of a low joint count scoring system during follow-up US may have underestimated disease activity in patients who presented a larger number of swollen and tender joints at baseline; furthermore, subclinical joint involvement could be missed at the 3-month follow-up, and adjustment of therapy could be delayed.

In conclusion, the use of reduced assessments, such as a 6-joint count, in the PDUS evaluation of RA patients is a useful and feasible method for evaluating the real status of inflammation and for monitoring the response to treatment during active disease. In patients in clinical remission, this count may be useful in analysing the presence of real remission and evaluating the response to treatment. PDUS in target joints is a feasible method complementary to

clinical assessment for guiding the clinician in the appropriate therapeutic decisions.

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