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Research Article

Ultrasound Evaluation of Rheumatoid Arthritis Patients in Clinical Remission: Is This a Real Remission?

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Abstract

Objective: With B-MODE and Power Doppler (PD) ultrasound examination (US) we can deepen the clinical and laboratory evaluation, defining the remission more stringently. The aim of the study was to evaluate the presence of subclinical disease activity in RA patients in clinical remission according to DAS28 criteria to detect early patients at risk of worsening.

Methods: We included patients over the age of 18 years affected by RA. Of these we considered in the study only the patients receiving sDMARDs, without concomitant bDMARDs therapy in clinical remission for at least 6 months, according to DAS28 criteria. We retrospectively collected clinical, laboratory and instrumental data of all the patients; finally, they were summoned for an ultrasound examination of their hands and feet according to the Backhaus score to evaluate disease activity. In addition, we evaluated tenosynovitis involvement in all patients.

Results: 40 patients were included in the study; 11 (27.5%) were PD+ (subclinical disease activity). In this sub-group Anti-Citrullinated Protein Antibody (ACPA) positivity and age were the more frequent prognostic factors of synovitis PD+, next to statistical significance. Clinical evaluation using other composite indexes (SDAI, CDAI) did not make the remission more stringent.

Conclusions: This study confirmed that the only clinical and laboratory data, including composite indexes usually used, are not sufficient to confirm deep remission state, especially in elderly patients ACPA positive. Moreover, our data demonstrated that US examination has more sensitivity compared to the simple clinical evaluation.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive damage of synovial-lined joints and variable extra-articular manifestations [1]. The therapeutic approach provides an increasingly early and aggressive treatment as it is evident that an early intervention can reduce or stop the progression of the disease [2]. There are numerous drugs available for the treatment of RA and include conventional synthetic and biologic Disease Modifying Anti-Rheumatic Drugs (csDMARDs and bDMARDs). Early treatment, the availability of biologic therapies and treat-to-target strategies have made the remission a realistic goal in RA [3-7]. However, most patients are still on treatment with only csDMARDs, both because they have obtained a good clinical response to this therapy so that a biological therapy is not considered necessary or because they have contraindications for biological agents (i.e. infectious diseases, cancer) [8].

The sDMARDs continue to be the first-line treatment for both the favorable risk-benefit profile and the pharmacoeconomic aspect and in many patients, are sufficient to achieve remission [9]. Accurate assessment of disease activity and joint damage in RA is important for monitoring treatment efficacy and for prediction of the outcome of the disease [10,11]. Different composite clinical indices are now available to monitor the disease activity and treatment efficacy [12]. But are clinical and laboratory parameters sufficient to establish whether the inflammatory process is stopped and thus exclude unfavorable progression over time [13]? It is essential to answer this question to properly guide therapy in

individual patients during follow-up in order to prevent relapse and ensure the best possible long-term outcome. In fact, as shown by various studies, some patients considered to be in remission on the basis of DAS28 score (DAS 28<2.6), the most commonly used criteria in clinical practice, show frequent reactivations of the disease and/or a progression of structural joint damage [14]. The last is one of the most important consequences of active disease and it can lead to joint deformities and functional limitation [15].

The Ultrasound Examination (US) responds to the need to deepen the clinical and laboratory evaluation, helping to define the remission more stringently, so that the concept of "Deep Remission" has recently been introduced to indicate the ultrasound remission. Today we have ultrasound instruments with an increasing sensitivity in detecting morph-structural joint alterations in RA, such as thickening of the synovial membrane, cartilage damage, bone damage and tendon commitment. In particular, alongside the Power-Doppler ultrasound technique (PD), it is possible to distinguish the joints with active synovitis from those in which inflammation has been stopped [16-19].

The primary objectives of this study are to:

- evaluate the presence of subclinical disease activity, through US study, in patients in clinical remission according to DAS28 criteria, in order to obtain an early identification of subjects with a high probability of future evolution of structural damage;

- identify the main clinical and laboratory predictors for failure to reach a state of deep remission (confirmed on ultrasound).

- The secondary objectives are to:

- assess whether other remission scores are actually more accurate (SDAI, CDAI, BOOLEAN) to exclude subclinical activity;

- evaluate the "Janus" contribution of steroids in disease activity: they can be necessary but not sufficient for the clinical assessment of the disease, but, on the other hand, they can be a source of potential false negative in PD US evaluation.

Materials and Methods

Patients

We retrospectively reviewed all patients aged over 18 years affected by RA who were referred to the Rheumatology Department in Brescia (Italy) during the period from 01/01/2015 to 28/02/2015. Of these patients, we considered only those who met the 2010 ACR/EULAR classification criteria of RA and who were being treated with csDMARDs (methotrexate, MTX; sulfasalazine, SSZ; leflunomide, LEF; hydroxychloroquine, HCQ); concomitant treatment with bDMARDs was an exclusion criterion of the study. We finally considered only those who met DAS remission criteria (DAS28 <2.6) for at least 6 months. Based on the medical records of each patient included in the study, we considered different parameters, that we can subdivide into: clinical and demographic; laboratory and instrumental data.

Clinical and Demographic Evaluation

About clinical data, we retrospectively collected data about the duration of the disease, the number of swollen and tender joints and the judgment of physician and patient about the degree of overall disease activity, expressed by analogue scale (VAS medical doctor and VAS patient, respectively). The latter data were evaluated at the onset along with the follow-up of the patient, up to 84 months after the first evaluation (every 6 months for the first year and every 12 months after that) and were used to calculate the composite index of disease activity, such as DAS28, SDAI and CDAI. Moreover, we evaluated the age, the biometric indexes (BMI), concomitant therapy with csDMARDs and steroids, with the respective dosages, smoking status, the presence of any comorbidities and concomitant therapies (focusing mainly on statins and ACE -inhibitors for the documented anti-inflammatory effect), the presence of extra-articular involvement and the level of functional disability by the Health Assessment Questionnaire (HAQ). According to literature we considered patients in remission if DAS28 <2.6; other remission criteria used during statistical evaluation was the following: SDAI <3.3, CDAI <2.3 and Boolean criteria.

Laboratory and Instrumental Evaluation

Concerning the laboratory data, we examined whether patients were rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) seropositive and their title, stratifying between low level (<3x normal range) and high level (> 3x normal range), as well as the positivity of the other main autoantibodies: Anti–Nuclear Antibodies (ANA), anti-native DNA antibodies (dsDNA), antiextractable nuclear antigens (ENA) and antiphospholipid antibodies (anti-cardiolipin and antibeta2glicoprotein I, lupus anticoagulant). We also collected data about the main values of inflammatory markers, C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR), from the onset and subsequent assessments.

Finally, from the instrumental point of view, we evaluated the presence or absence of marginal erosions by traditional radiography and the possible progression of structural damage during follow-up. All clinical, laboratory and instrumental data were collected by rheumatologists who did not perform the US evaluation.

Ultrasound Evaluation

All patients were subjected to US, according to the Backhaus score, of the following joints: wrist, Metacarpophalangeal (MCP) II, MCP III, Proximal Interphalangeal (PIP) II, PIP III, Metatarsophalangeal (MTP) II, MTP V. For each joint, evaluated bilaterally, we evaluated the presence of joint effusion and synovial hypertrophy (grading from 1 to 3 according to the Scheele method), the degree of synovial vascularization with PD (grading from 1 to 3 according to the Szkudlarek method), the presence of marginal or subchondral erosivity (dichotomous rating). In addition, we evaluated the presence of tenosynovitis (dichotomous rating). For each joint area we performed both axial and coronal evaluations, studying the dorsal (all), volar (all) and lateral-medial (wrist, MCP II, PIP II, PIP III, MTP V) sides [20-22].

According to the OMERACT guidelines, the US study was performed by an independent expert rheumatologist in musculoskeletal ultrasound who was unaware of the clinical evaluation (blind). For all the feedback, we used the latest generation ultrasound scanner (Esaote MyLab 70 X vision), with multi-frequency linear probe (6-18 MHz). For the study in B-MODE we used this setting: frequency of 18 MHz; gain of 50%; the PD frequency was 10 MHz, the PRF (pulse repetition frequency) was 750 Hz. The study included a period of 15-20 minutes for each patient; all the US were performed in the morning. If a synovial hypertrophy PD+ with grading> 1 in at least 2 joints resulted, the patient was not considered to be in deep remission (subclinical disease activity).

Statistical Evaluation

Data were analyzed using the following statistical tests:

- $\chi 2$ test with Fisher's correction, used to compare qualitative parameters;
- Mann-Whitney test, to compare the quantitative parameters.

We used these two non-parametric tests because the samples in the study were small in size (<30 patients each) and the distribution of the samples was not normal. A p value <0.05 was considered as statistically significant.

Results

Demographic and Clinical Features

There were 575 patients over the age of 18 with RA who were evaluated in the Rheumatology Department in Brescia (Italy) in the January-February 2015 period. Of these, 388 were receiving bDMARDs and 187 csDMARDs; we considered only the latter in the study. Of the 187 patients receiving csDMARDs, 98 were found to be in clinical remission according to DAS criteria (DAS28 <2.6). Among these, 40 patients who met the criteria diagnostic ACR / EULAR 2010 at the time of diagnosis were randomized and summoned to undergo an ultrasound examination of their hands and feet.

Patients included in the study had an average age of 64 and were represented by 70% women (F/M:28/12). Most were FR (70%) and ACPA (73.68%) seropositive, although data relating to this last item was missing in 2 patients. In 33 patients (82.5%) the diagnosis of disease was made within two years from the clinical onset (early arthritis); the mean disease duration was 11.8 months. All patients were in DAS28 remission for at least 6 months (inclusion criteria) but 9 subjects (97.5%) for at least 1 year (mean 1.65). The mean values of the other two composite indices, SDAI and CDAI, were respectively 3.28 and 2.75. 50% of patients also respected the Boolean remission criteria.

The demographic and clinical features of the analyzed sample are reported in Table 1 and Table 2 respectively.

Age, median and interquartile range [0,25-0,75]	66,5 [56,75-72,25]
Gender (F:M)	28:12:00
Female, n (%)	20/40 (70%)
BMI, median and interquartile range [0,25-0,75]	24,79 [23,005-27,785]
Smoke, n (%)	14/37 (37.84%)
ANA +, n (%)	17/33 (51.51%)
FR +, n (%)	28/40 (70%)
High level RF, n (%)	13/40 (32.5%)
ACPA +, n (%)	28/38 (73.68%)
High level ACPA +, n (%)	25/38 (65.78%)
Early arthritis (onset < 2 years), n (%)	33/40 (82.5%)
Onset > 2 years, n (%)	7/40 (17.5%)
Onset-diagnosis interval (months), median and interquartile range [0,25-0,75]	6,5 [2,75-12]

BMI: Body Mass Index
ANA: Antinuclear Antibodies
RF: Rheumatoid Factor
High level RF: RF value 3 times higher compared to the maximum limit of normal range
ACPA: Anti-citrullinated Peptide Antibodies
High level ACPA: ACPA value 3 times higher compared to the maximum limit of normal range

Table 1: Demographic and laboratory features of the patients at the time of US evaluation.

DAS 28, median and interquartile range [0,25-0,75]	1,66 [1,35-1,8875]
SDAI, median and interquartile range [0,25-0,75]	2,61 [0,95-5,125]
CDAI, median and interquartile range [0,25-0,75]	2 [0-5]
Boolean (%)	50%
CRP (mg/L), median and interquartile range [0,25-0,75]	1 [1-5,275]
HAQ, median and interquartile range [0,25-0,75]	0,5 [0,09375-0,75]
Duration of remission (months), median and interquartile range [0,25-0,75]	37,5 [16-68,5]
Diagnosis-remission interval(months), median and interquartile range [0,25-0,75]	12 [6-24]
Duration of remission < 12 months, n (%)	1/40 (2.5%)
Duration of remission > 12 months n (%)	39/40 (97.5%)

DAS: Disease Activity Score
SDAI: Simplified Disease Activity Index
CDAI: Clinical Disease Activity Index
CRP: C-Reactive Protein
HAQ: Health Assessment Questionnaire

Table 2: Clinical features of the patients in the study at the time of US evaluation.

Pharmacological Features

At the time of evaluation, 65% of patients were receiving MTX, 37.5% HCQ, 7.5% LEF, at a mean dosage of 10.67 mg/week, 186.66 mg/day and 13.81 mg/day respectively. No one was taking SSZ. 67.5% of patients were also taking steroids, at a mean dosage of 23.85 mg/week. Only 4 patients were treated with steroids at higher dosage (> 35mg/week).

The pharmacological features of studied patients are reported in Table 3.

Steroids, n (%)	27/40 (67.5%)
Steroids (mg/week), median and interquartile range [0,25-0,75]	25 [20-25]
Cortisonici < 35 mg/week, n (%)	23/27 (85.18%)
Cortisonici > 35 mg/week, n (%)	4/27 (14.8%)
MTX, n (%)	26/40 (65%)
MTX (mg/week), median and interquartile range [0,25-0,75]	10 [10-12,5]
LEF, n (%)	3/40 (7.5%)
LEF, median and interquartile range [0,25-0,75]	11,43 [10,715-15,715]
SSZ, n (%)	0
SSZ (mg/die), median and interquartile range [0,25-0,75]	0
HCQ, n (%)	15/40 (37.5%)
HCQ (mg/die), median and interquartile range [0,25-0,75]	200 [200-200]

MTX: Methotrexate
LEF: Leflunomide
SSZ: Sulfasalazine
HCQ: Hydroxychloroquine

Table 3: Pharmacological features of patients at the time of US evaluation.

Sonographic Features

Ultrasound investigation carried out on 14 joints provided by the Backhaus score showed that 38 patients had B-MODE synovitis at least in one joint (with a range of joints involved ranging from 1 to 12), 32 at least an eroded joint (range: 1 -8) and 15 showed at least one PD+ synovitis (range 1-11). The mean number of involved joints for each patient was 4.13, considering B-MODE synovitis, 3.65 with regards to the erosions and 3.06 for PD +. Two patients with PD + synovitis had both hands and feet involvement (II MTF and / or V MTF); no patients had PD + synovitis instead synovitis exclusively in the feet.

There were 23 patients that had both DAS28 <2.6 and SDAI <3.3 (57.5%) and 11 (47%) of these showed positivity of the PD signal to at least one of the joints examined (range: 1 -11), with a mean value of 3.27 joints per patient; similarly, in patients with CDAI <2.3 the mean of PD positive joints for each patient was of 3.18. Of the 20 patients in Boolean remission, 8 (40%) showed joints with PD positive signal, between a minimum of 1 and a maximum of 5 joints involved (mean of 2.37 joints per patient). 15% of the patients also had tenosynovitis, but this was never found in the absence of joint involvement. In particular, the flexor tendons were involved in 5 patients (12.5% of the cases); the extensor tendons in 2 patients (5% of cases).

The US characteristics of the studied sample are summarized in (Table 4).

>1 US-S, n (MIN-MAX)	38 (1-12)
US-S + joints/patient	4.13
US-S only feet, n	0
>1 US-E, n (MIN-MAX)	32 (1-8)
US-E+ joints/patient	3.65
US-E only feet, n	1
>1 US-PD, n.(MIN-MAX)	15 (1-11)
US-PD + joints/patient	3.06
US-PD only feet, n	2
US-PD in patients with SDAI<3.3, n (MINMAX)	11 (1-11)
US-PD in patients with SDAI<3.3, mean	3.27
US-PD in patients with CDAI<2.3 n, (MINMAX)	11 (1-11)
US-PD in patients with CDAI<2.3, mean	3.18
US-PD in patients Boolean, n (MIN-MAX)	8 (1-5)
US-PD in patients Boolean (mean)	3.27
Tenosynovitis, n (%)	6/40 (15%)
Flexor tendons, n (%)	5/40 (12.5%)
Extensor tendons, n (%)	2/40 (5%)
Only tenosynovitis, n (%)	0

US-S: Ultrasound Synovitis
US-E: Ultrasound Erosion
US-PD: Ultrasound Power Doppler Signal
(MIN- MAX): Minimum and maximum number of involved joints

Table 4: US features of studied patients.

Considering the patients with PD positive signal associated with synovitis, the most involved joints were the right MCP II (72.7%), the left MCP II (54.5%) and the left wrist (45.4%), as indicated in Table 5.

Joints	US-PD +, n (%)	US-PD score, mean + SD
Right wrist	3 (27.3%)	1.67 ± 1.15
Right MCP II	8 (72.7%)	2.12 ± 0.99
Right MCP III	3 (27.3%)	2 ± 1
Right PIP II	2 (18.2%)	2 ± 1.41
Right PIP III	2 (18.2%)	1 ± 0
Right MTP II	2 (18.2%)	1 ± 0
Right MTP V	2 (18.2%)	2 ± 0
Left wrist	5 (45.4%)	1.6 ± 0.55
Left MCP II	6 (54.5%)	2.17 ± 0.75
Left MCP III	4 (36.4%)	1.25 ± 0.5
Left PIP II	1 (9.1%)	2
Left PIP III	2 (18.2%)	1.5 ± 0.71
Left MTP II	3 (27.3%)	1.33 ± 0.58
Left MTP V	3 (27.3%)	1.33 ± 0.58

MCP: Metacarpophalangeal
PIP: Proximal Interphalangeal
MTP: Metatarsophalangeal
US-PD score: score for the PD signal detected

Table 5: PD + signal and mean intensity of the signal in studied joints.

Based on US criteria the patients were divided into two groups: subjects with PD + synovitis (PD+) and subjects with PD-synovitis or absence of synovitis (PD-). The first group was represented by those who had at least 2 joints with PD positive signal in the ultrasound examination and included 11 patients (27.5%), the second included the remaining 29 patients. We considered patients with one single joint involved as negative so as to be even more stringent in our evaluation, avoiding the possibility of any false positives. Thus, 27.5% of the patients have actually shown subclinical disease activity.

Demographic, Clinical and Pharmacological Features Comparison

Each group was stratified for all demographic, clinical, pharmacological and US parameters. With regards to the demographic and clinical aspects there were no significant differences (p>0.05). Only for the age and the ACPA seropositivity (especially at high level) there was a tendency to statistical significance.

The two groups were homogeneous with regards to the ongoing drug treatment, both for csDMARDs and steroids. Significant differences between the two groups were found in US results, especially in the median number of synovitis and eroded joints for each patient (p <0.05), in both cases higher in the positive PD group (Table 6).

Ultra-sonographic	PD +	PD -	P value
US-S > 1, n (%)	11/11 (100%)	27/29 (93.1%)	0.5205
US-S/pz.	6 [4.5-7,5]	3 [1-4]	0.0003
US-S only feet, n (%)	0	0	-
US-E > 1, n (%)	11/11(100%)	22/29 (75.86%)	0.0837
US-E/pz.	4 [3.5-7]	2 [1-3]	0.0017
US-E only feet, n (%)	1/11 (9.09%)	0	0.275
Tenosynovitis, n (%)	3/11(27.27%)	4/29 (13.79%)	0.2857
Flexors tenosynovitis, n (%)	2/11(18.18%)	3/29 (10.34%)	0.4225
Extensors tenosynovitis, n (%)	1/11 (9.09%)	1/29 (3.45%)	0.4795
Only tenosynovitis, n (%)	0	0	-

Table 6: Ultra sonographic features of PD + e PD – patients.

The data are expressed as median and interquartile range [0,25-0,75] if not specified.

Discussion

Recent studies have shown a greater sensitivity of ultrasound (US) with respect only to the clinical evaluation in the detection of joints structural abnormalities and inflammatory activity. It has also a higher predictive value with regards to patient outcome in terms of erosivity and disease reactivation [23,24]. With our study we evaluated the status of "Deep Remission" in RA patients treated with csDMARDs, considered in remission on the basis of DAS criterion [25]. The Backhaus score (assessed on large series) was used for US evaluation and particular emphasis was given to the PD signal associated with synovitis, parameter by which we have obtained two samples of subjects, positive Power-Doppler (PD +) and negative Power-Doppler (PD-)patients. The first group included patients with two or more joints with synovitis associated with PD signal the second those with less than two joints involved (the latter represented the control population). Considering negative even those patients who showed only one articulation PD+ we wanted to be as stringent as possible, minimizing the false positive.

The results show a homogeneity of the two samples regarding demographic, clinical and pharmacological features. There were no significant differences regarding steroids therapy and its dosage. As to this aspect, it should be stressed that the majority of our patients were in the low dose steroids despite the state of clinical remission (<5mg / day) and the dosage of csDMARDs (MTX, LEF, HCQ) was in most cases submaximal. Also composite indexes with which we evaluate the disease activity (DAS28, SDAI, CDAI) in daily practice were not significantly different in the two groups of patients and therefore not able to identify patients PD +. This could be related to the fact that they consider the patient's judgment about the activity of the disease based on a visual analogue scale of pain difficult to confirm objectively. But we must highlight the fact that seropositivity to ACPA, especially at high level, is more frequent in PD + showing a trend to statistical significance, that was not

reached probably because of the low number of the sample. Most joints affected by synovitis accompanied by PD signal were found to be the right MCP II and the left MCP II, in which the PD signal also had a greater intensity, and this can be associated with greater use of the same in everyday life.

The left wrist appears frequently involved and this aspect could be an interesting topic for discussion given the greater number of right-handers in the population. Our study, like many other studies, confirms a higher prevalence of smoking than expected. In light of the results obtained with our study, we can say that the only clinical and laboratory data, including composite indexes usually used, are not sufficient to confirm deep remission state. In particular, the greater ultrasound examination sensitivity compared to the simple clinical evaluation is confirmed. This suggests an important role of this examination in the monitoring of patients with RA. 27.4% of the patients in fact showed the presence of inflammatory activity despite the clinical evaluation having classified them as patients in remission. We had optimized the drug therapy and intensified the US follow-up in these patients.

The US evaluation is a non-invasive examination, very well tolerated by patients and relatively inexpensive. However, it is an operator-dependent examination and there is still no standardized score for his performance [26]. The use of the Backhaus US score in which the joints mainly affected by inflammatory activity are included reduces the time required for the ultrasound examination requiring an average of 15 minutes for each patient, but at the same time allowing an accurate evaluation [27]. Our pilot study had some limitations: the low number of samples; unavailability of some laboratory data (not available from the medical records of some patients); moreover, it was a retrospective study and not prospective. Despite these limitations, which will be subject to future revaluations the study leads us to conclude that the use of joint ultrasound examination is essential in the periodic monitoring of disease activity. In fact, this could early identify patients who might otherwise be mistakenly considered in remission, with consequent reduction of immunosuppressive therapy. In addition, it would allow us to optimize the therapeutic strategy in patients where subclinical disease activity is detected.

In the future, it would be useful to explore the predictive significance of ACPA positivity, especially at high level, recruiting a larger number of patients. This would allow to further optimize the monitoring of RA patients, both in terms of cost and time.

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