Original papers

Med Ultrason 2018, Vol. 20, no. 3, 328-334
DOI: 10.11152/mu-1384

Does patients' opinion of remission in rheumatoid arthritis overlap ultrasound "true" remission? – a pilot study

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Abstract

Aim: Patients describe rheumatoid arthritis (RA) remission as the absence of any symptoms or return to normality. Residual ultrasound (US) synovitis was frequently described in remission cohorts in previous studies. US tenosynovitis evaluation and scoring seems to better follow clinical remission scores compared with synovitis in RA. Our objective was to verify the presence of US findings suggestive of persistent inflammation in a cohort of patients in remission according to their own opinion. **Materials and methods:** Forty-three RA patients were prospectively enrolled in this pilot study between 2015-2017 according to their positive answer to the question "Are you feeling free of symptoms, just like before your RA symptoms started?". Clinical evaluation of tender and swollen joints was performed in the same day with US evaluation of 24 joints and 26 tendon sites and lab C-reactive protein (CRP) evaluation. DAS28-CRP and SDAI were calculated. **Results:** A total of 72.9% (35 of 43) of patients were in remission per DAS28 criteria. Except for CRP value, no other variables were significantly different in the 35 of 43. PD scoring in tenosynovitis of the ankle and feet was 100% overlapping remission felt by patients. PD tenosynovitis in both upper and lower limbs was found in less than 10% of patients, and only grade 1 (minimal). **Conclusion:** A combination of patients' opinion and PDUS evaluation could be a starting point for RA treatment tapering.

Keywords: ultrasound; rheumatoid arthritis; patient related outcomes; treatment tapering

Introduction

Remission is the main goal of rheumatoid arthritis (RA) treatment. Cartilage and bone permanent destructive damage are fearful consequences of longstanding disease activity. Quantifying the amount of RA inflammation is feasible through clinical indices [1-4]. Same parameters are usually used to define remission. No "gold standard" RA remission definition is currently available. Reported remission rates in previous cohorts are variable, depending on the remission definition used. American College of Rheumatology (ACR) remission definition [1] was found the most stringent one (less remission rates among patients), and Disease Activity Score DAS 28 [2] the most liberal one (high remission rates). Other indices (Clinical Disease Activity Index – CDAI, Simplified Disease Activity Index – SDAI, Routine Assessment of Patient Index Data – RAPID3) are situated in between ACR and DAS 28 on remission definition grounds [5]. In the biologic therapy-era today, the percentage of patients achieving remission has improved considerably. DAS28 as remission index showed insufficient construct validity [6]. SDAI is increasingly implemented in remission definition with a <3.3 value [3].

As clinical criteria of defined remission were proven insensitive in detecting low but clinically significant joint level of inflammation, imaging was added for improvement [7-11]. Ultrasound (US) is an imaging procedure that is patient friendly, non-invasive, repeatable and offers "blitz images" of joint activity, especially with Doppler investigation. Power Doppler (PD) activity is the best predictor of further joint damage in remission RA patients- the so called subclinical synovitis [8]. The absence

Received 22.12.2017 Accepted 23.02.2018
Med Ultrason
2018, Vol. 20, No 3, 328-334
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of both grey scale (GS) and PD synovitis in dominant hand metacarpophalangeals (MCPs) 2-5 and wrist was defined as "strict remission" [7,11]. US is also mandatory to differentiate synovitis from tenosynovitis in swollen joint areas. Recently, tenosynovitis in RA patients was proven to have the same sensitivity to change as synovitis [12-15] and was established as predictor for erosive disease in early RA [16]. Moreover, in recent studies, PDUS active tenosynovitis was barely found in patients in remission according to DAS 28 and SDAI [13,15].

Patients' opinion on their own state of disease is incorporated in RA evaluation and in disease quantification indices. Patient Reported Outcomes (PROs) were found as relevant as clinical and laboratory evaluations in disease status assessment [5,17-21], adding a personal subjective touch to a scientific description of RA. A patient can clearly feel better than any index if their disease is "as good as gone".

Patients describe remission as the absence of symptoms and the feeling of the "return to normality" [17,18]. As the return to normality would be the ideal of a remission definition, it became interesting to test a feed-back strategy,and calculate clinical and US indices in RA patients feeling as close to normal as possible.

The aim of the current pilot study is to investigate, in a cohort of patients in remission according to their own opinion, the presence of US findings suggestive of persistent inflammation: subclinical synovitis and tenosynovitis in areas frequently involved in RA. Also, the study evaluates some areas poorly graded with USin RA studies so far.

Material and methods

Forty-eight RA patients were prospectively enrolled in one center in this cross-sectional study between 2015-2017 according to their positive answer to two questions "*Are you feeling free of symptoms, just like before your RA symptoms started?"* and *"How long have you felt this way?*" Remission duration was quantified with the second question. Written informed consent from all patients and local Ethics Committee approval were obtained. Subjects were recruited from the outpatient clinic. All patients were on drugs known for their ability to modify disease activity (DMARDs) at the evaluation time. Patients with concurrent diseases that could alter pain subjective evaluation (osteoarthritis, low back pain, fibromyalgia, depression) were excluded. The confirmation of their positive answer to the initial question was translated in a patient VAS=1 (visual analogic scale quantifying, with a number from 1 to 10, patients' opinion regarding their disease activity). Patient's VAS is currently included in DAS28-CRP (C Reactive Protein) and SDAI indices calculation. Physician's opinion, also included in indices calculations, was also quantified with VAS=1 (on a scale from 1 to 10), for all included patients.

Demographic characteristics of patients were recorded: age, sex, disease duration, appreciation of remission duration in their own opinion, treatment. Clinical evaluation of tender and swollen joints was then performed by an independent assessor. The same day US evaluation was performed by an ultrasonographer with more than 10 years of experience. US evaluation was blinded to clinical evaluation and included 24 joints [carpal, metacarpophalangeals (MCPs) 2-5, tibiotalar, subtalar, metatarsophalangeals (MTPs) 1-5 bilaterally] and 26 tendon sites (carpal extensors 4th and 6th, finger flexors 2-5, tibialis posterior, peroneal, plantar flexors 1-5 bilaterally). The areas were chosen considering their frequent involvement in RA (wrist, hand and feet joints and tendons), but adding a few rarely explored areas in RA, that might hide subclinical pathology (subtalar joint, plantar flexors). All US examinations were performed on an Esaote My Lab 70 machine, equipped with12-18 MHz linear transducer and included GS and PD evaluations. US evaluations were performed according to international published guidelines [22]. For hand joints, both dorsal and volar scans were taken and the highest pathologic finding was graded. Tendons were scanned in longitudinal and transverse plans in all their length, grading the highest tenosynovitis point. Both GS and PD lesions, for joints and tendons, were quantified using semi-quantitative grading: grade 0=normal, grade1=minimal, grade 2=moderate, grade 3=severe [23,24]. For PD evaluations, the same characteristics of the machine were kept throughout the study: Pulse Repetition Frequency (PRF) 0.5, Wall Filter (WF)1 (lowest possible), Doppler frequency adjusted to GS frequency, Doppler gain adjusted to the absence of signals inside bone. As all patients were in remission, grade 1 was thoroughly weighted, considering the possible GS and PD artifacts in explored areas (retinaculae, nutritive vessels).

Lab CRP evaluation was performed the same day. DAS28-CRP and SDAI were calculated after clinical and US evaluations, counting VAS=1 for both physician and patients.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp USA). Data is presented as mean±standard deviation(SD) or mean (confidence interval) (CI). Values for $p<0.05$ were considered significant. The Student's t test was used for the evaluation of the total dataset. A bootstrapping procedure was executed to obtain 95% CI.

Results

Five patients out of 48 were excluded from calculations due to low dose cortico-therapy at the evaluation time. All patients were on DMARDs therapy and 24 of 43 were also on biologic therapy. Mean age was 60.84 (range 21-75) and 6 of 43 were male. Mean disease duration was 78.21 months (range 2-350) and mean remission duration (approximation of patient's opinion) was 21.19 months (range 1-120).

For all 43 patients DAS 28 CRP 4 variables was calculated. After calculation, the initial cohort was split into 2 cohorts, cohort 0 with DAS 28 >2.6 (no overlapping remission) and cohort 1 with DAS 28 <2.6 (overlapping remission). Demographic characteristics of patients in the two cohorts are detailed in table I. Out of the 43 patients, 35 (72.9%) were in cohort 1. All calculations were made separately for the 2 cohorts, to depict the differences. No statistically significant differences considering demographical data between cohorts were found, except for the mean value of CRP and disease duration ($p<0.05$).

Regarding subclinical synovitis and tenosynovitis, figures 1 and 2 reveal their distribution (PD and GS, respectively) among studied joints and tendons areas. Most residual synovitis was foundduring GS evaluation in the carpal joints (43 out of 86 carpal joints on both sides- 50%), followed by MTPs. Six carpal joints (6 of 86-0.06%) had a grade 3 synovitis on GSUS evaluation. On PD evaluation, carpal joints were found positive on 17 of 86 joints (19.7%), with only 4 joints (4.65%) with a grade of 2, followed by MTP1. No grade 3 on PD was found.

Subclinical tenosynovitis, both in GS and PD, were found much less frequentlythan synovitis. Most GS teno-

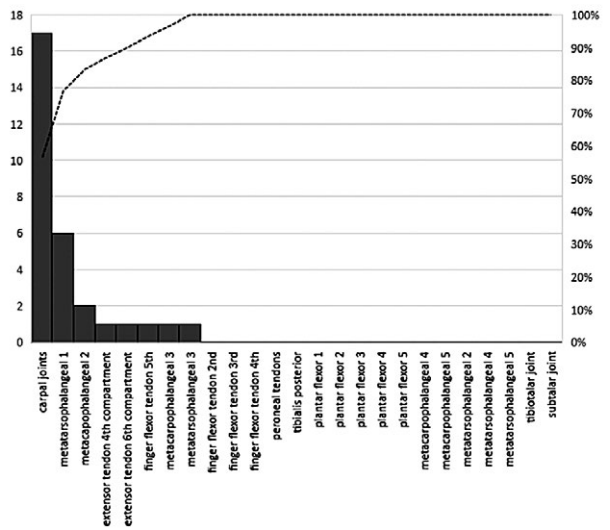

Fig 1. Distribution of power Doppler ultrasound (PDUS) positivity graded 1 and 2 among studied areas (joints and tendons).

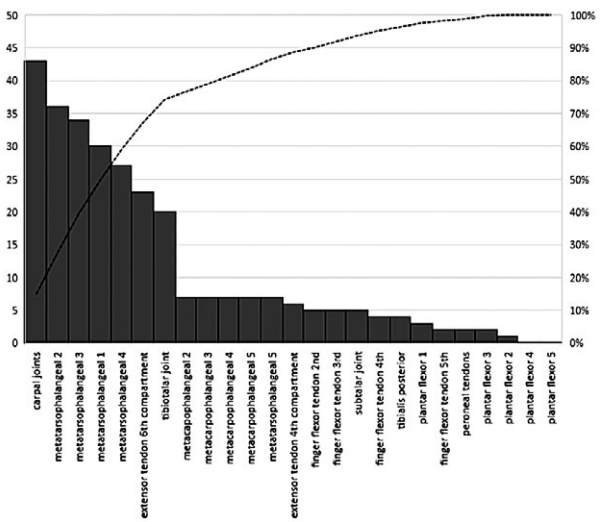

Fig 2. Distribution of grey scale ultrasound (GSUS) positivity graded 1,2 or 3 among studied areas (joints and tendons).

Table I. Patients' characteristics after splitting into 2 cohorts: remission status 0 (DAS28>2.6) and status 1 (DAS28<2.6).

	Remission status	N	Mean±SD	p value
Age	0	8	58±10.89	Not sig
	1	35	61.49±13.585	
Tender joint count	0	8	2.50±.756	Not sig
	1	35	.66±.938	
Swollen joint count	0	8	2.13±1.246	Not sig
	1	35	.43±.884	
CRP (mg/l)	0	8	11.0±10.3236	<0.05
	1	35	3.485±6.3422	
Disease duration	0	8	116.63±113.169	<0.05
	1	35	69.43±54.273	
Remission duration	0	8	23.00±20.501	Not sig
	1	35	20.76±22.672	

CRP – C Reactive Protein; N – number of patients; SD – Standard Deviation

Table II. Prevalence of US remission in patients with clinical remission – bootstrapping for Confidence Interval.

Ultrasound remission	DAS28-CRP remission	SDAI remission
PD tenosynovitis	94.3 (5.7-100)	90.9 (77.3-100)
GS tenosynovitis	57.1 (40.0-74.3)	54.5 (36.4-72.7)
PD synovitis	62.9 (45.7-80.0)	59.1 (36.4-77.3)
GS synovitis	17.1 (5.7-31.7)	13.6 (0-31.8)
PD lower limb tenosynovitis	100 (100)	100 (100)
GS lower limb tenosynovitis	91.4 (82.9-100)	86.4 (72.7-100)

PD, Power Doppler; GS, Grey Scale; DAS 28, Disease Activity Score including 28 joints; CRP, C Reactive Protein; SDAI, Simplified Disease Activity Index.

synovitis was found on 6th carpal extensor compartment (23 of 86, 26.7%) with grade 3 found in a single case. PD evaluation on tendons revealed a very low positivity, and the only affected areas were carpal extensors compartments 4th and 6th (each with one tendon with grade 1) and finger flexor 5th (also one tendon grade 1). No grades 2 or 3 were found.

The overlapping rate of US remission (no GS and/or PD activity) with clinical remission scores was then calculated. Residual GS synovitis was the main finding (overlapping remission in only 17%). PD synovitis remission was overlapping DAS 28 remission in over 62%. GS tenosynovitis in upper limb was a frequent finding (mostly at the 6th compartment and the finger flexors). There was no PD signal found on the lower limb examined tendons (ankle and plantar flexors). Overall, PD tenosynovitis remission was overlapping DAS28 and SDAI remission in more than 90% of examined cases (table II).

PD scoring in tenosynovitis of the ankle and feet was the ideal (100% overlapping with patients' opinion) and the furthest from ideal was GS synovitis in superior and inferior limbs (mean 17.1%).

Discussions

To the best of our knowledge, this is the first study to describe US subclinical synovitis and tenosynovitis in a cohort of RA patients in remission according to their own opinion. Patient's VAS on global assessment of disease activity is incorporated in remission indices of RA. However, there is no consensus on the cut-off – VAS<=1 might be too restrictive and there might be discordance between patient VAS and physician VAS. Also patients' age and concurrent diseases might alter patients' opinion regarding their pain [6,8,17-21,25]. The novelty of our study is the change of the inclusion criterion in the study cohort to one not quantified by a number, but by a general characterization of "return to normal" state.

Treating RA to target remission is a main concern for rheumatologists, but it has also been characterized as "just aspirational" [26-28]. EULAR newest set of recommendations include algorithms for best standardization of RA treatment and follow-up [27,29]. Remission state should exclude further progression of joint destruction. Subclinical US findings, especially PD activity, were pointed out as the possible main cause for perpetuating joint destruction in patients considered as having achieved remission [8]. PD activity evaluation alone could identify patients with RA in clinical and histologic remission [30,31]. The proportion of subclinical synovitis found with US in various cohorts of patients in remission according to usual indices varied between 20-50% for moderate PD activity (grade 2) to over 80% for GS synovitis which is constantly the most encountered finding in remission patients [3,7,32]. GS synovial hypertrophy alone seems to be linked to fibrotic intraarticular tissue in old disease and was not linked to histologic inflammatory activity in a recent validity study [31]. Only PD subclinical synovitis is significant for disease progression. In a recent study [33] focusing on RA patients in remission on DAS 28 criterion, more PD signal was found on joints with previously detected bone erosions.

Subclinical tenosynovitis was only described so far in two US studies, both multi-center [13,15], expressing the same conclusion. Subclinical GS and PD tenosynovitis was significantly less encountered in remission patients than subclinical synovitis. STARTER study of the Italian Society of Rheumatology [15] enrolled 427 patients in remission according to clinical scores- out of the cohort, PDUS tenosynovitis remission was reported in 78% of patients, comparative to only 58% PDUS synovitis remission. This reference study involving 25 centers in Italy suggested that tenosynovitis could be more reliable for the description of remission than synovitis. On a previous smaller cohort, in a multicenter longitudinal study, our team found that tenosynovitis remission scores were overlapping clinical remission according to CDAI and SDAI in 100% of cases [13]. These results might be explained by the more superficial position of tendons comparative to joints (PD is more accurate in superficial structures).

The results of the current study are in concordance with previous studies. PD signal of the inferior limbs was absent in almost all cases, even in rarely explored areas,

such as plantar flexors. GS synovitis at carpal joints level and MTPs was the most encountered finding.

Inclusion of patients' perspective of remission in Clinical Practice Guidelines (CPGs) is highly recommended [19,34]. As patients refer to remission as a return to normal state, remission described by patients should involve no subclinical pathology. In an ideal situation, patients would have no pain/swelling of the joints, no imaging abnormalities and they would therefore be completely independent and live a normal life. The purpose of this study was to verify the accuracy of patients' described remission state by US visualization of joints' and tendons' subclinical pathology. US is known to better depict intraarticular pathology than clinical examination [35]. PDUS negative patients in clinical RA remission developed significantly fewer flares during the 12 months of follow-up than PDUS positive patients [30]. PDUS positive tenosynovitis showed a significant association with the flare questionnaire and further predicts an unstable remission [15].

The present cohort confirms the suppositions from previous cohorts. PD tenosynovitis in lower limbs (tibialis posterior, peroneal, plantar flexors) was 100% overlapping remission, regardless of the clinical scoring method used (DAS 28, SDAI). Also in upper limbs (extensor compartments 4 and 6, finger flexors), overlapping percentage was more than 90%.

The lack of statistically significant differences between cohorts 0 and 1 in our study shows that patients describe accurately their state. More than 70% of patients were found in DAS 28 criteria of remission cohort. The fact that DAS 28 includes CRP, which was the only value statistically different in the two cohorts might be a bias of the study (CRP might be elevated due to reasons independent of their rheumatic disease). Disease duration was also a factor of statistically significant difference – the older the disease, the higher the possibility of misinterpreting by the patient.

This study has a few strengths: it is the first study enrolling only patients that feel "back to normal", though experiencing the most accurate remission state (in their opinion). US was performed on joints and tendons mostly involved in RA. It is also the first study trying to depict the involvement of plantar flexors in RA activity state. Plantar flexors were excluded from other studies due to their position (feet synovitis, even PD positive, was not always linked to disease activity). Recently feet PDUS synovitis was found as a potential cause of misinterpreting remission (absence of feet in DAS28 score) [36]. In our study, MTPs were frequently involved, even PD positive. No PD positivity was found on plantar flexors. Ankle involvement in RA seems to also be underestimated- in a previous study, ankle abnormalities were found in >80% of RA active patients [37]. No PDUS ankle pathology was found in our cohort of patients. Regarding subtalar joint, 2/86 joints examined had a GSUS grade ≥1. The positivity of GS/PD US findings in MTPs support the previous observations, that MTPs can have US findings even in normal persons, due to their position and walking function.

The relatively small number of patients can be a limitation of this pilot study. Itis justified bythree reasons: firstly, all patients with associated pathology as osteoarthritis were excluded (confusing pain and "normal" life habits). Secondly, patients on corticosteroids were excluded, cortisone being known for reducing Doppler signal almost immediately after local/intravenous administration [38]. Also, corticosteroids might mask the subjective symptoms of RA, hiding the joint further destruction. Thirdly, for the accurate appreciation of physician VAS, all patients were recruited from the same physician database. Under these circumstances, the included patients had really no symptoms of disease, both in their opinion and their physician's. Nevertheless, RA activity can be silent. PDUS remains the best predictor of the continuation of destruction, even in patients living a normal life on treatment.

Conclusion

Patients' opinion of remission seems to better and easier characterize their actual state than clinical indices usually used in practice. PDUS tenosynovitis remission score overlaps almost perfectly the "return to normal" state of patients. A combination of patients' opinion and PDUS evaluation might be the winning combination of a remission definition and the starting point for treatment tapering. PDUS of the lower limb tendons can be considered as a validation method for the remission state. More studies are needed in this area, preferably multicentric, on a higher number of patients, to confirm this hypothesis.

Conflict of interest: none

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