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Validity of Remission Criteria in Rheumatoid Arthritis Compared to Ultrasound-Defined Remission

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Abstract

Objectives: Remission is the ultimate purpose of treatment in Rheumatoid Arthritis (RA). However, even when the most stringent composite scores were used, structural damages can occur. For that purpose ultrasonography (US) appears to be the best way to assess real remission. Our principal aim was to investigate the validity of different RA remission scores using the US as the reference. ***Methods:*** An analytic diagnostic study of 30 RA patients in remission according to DAS28 and a control group with active RA was conducted between January and October of 2018. Among them, we identified patients in remission according to the SDAI, the CDAI, and the ACR/EULAR remission score. The validity of each activity score for remission was calculated using as a gold standard the absence of PD signal. ***Results:*** All patients were in remission according to DAS28 with an average score of 2.03 [1.13-2.6]. US examination showed PD signals in 57% of all patients. Twenty-six patients were in remission according to CDAI, a Doppler signal was detected in 58% of those cases. SDAI remission was accomplished in 19 patients with PD activity in 53% of cases. For the 14 patients in remission according to ACR/EULAR criteria, synovial hyper-vascularization was found in 64%. Considering true remission as the absence of PD signals, the most sensitive and specific score

was DAS28 (93% and 68% respectively). ***Conclusion:*** Considering remission in RA as the absence of vascularized synovitis, the DAS28 was the most sensitive and the most specific score.

Keywords: Rheumatoid Arthritis, remission, ultrasonography, validity

Advances in knowledge

- Recent strategies have increased the potential to achieve low disease activity and remission thanks to ‘‘Treat-To-Target’’ and “Treat to Budget” strategies.
- Various composite outcome measures exist but structural damage occurs even when the most stringent ones are used.

Application to patient care

- Considering true remission the absence of PD signal, it is important to assess the validity of each disease activity score in obtaining remission.
- DAS28 score seems the most valid score to assess remission when the absence of PD signal is taken as reference.

Introduction

Achieving remission is the ultimate goal of treatment in Rheumatoid Arthritis (RA). In the past few decades, new therapeutic modalities and recent strategies have increased the potential to achieve low disease activity and remission by halting the inflammatory process. Indeed, a specific strategy of treating early RA adapted to each patient and including close follow-ups aiming for less disease activity and lower cost, called ‘‘Treat-To-Target’’ and “Treat-to-Budget” are now being implemented.[1] However, the concept of remission is complex as there is no consensual definition.[2] Taking into account clinical and biological criteria, several composite scores are available in daily practice. However, even when the most stringent ones are used, structural damage occurs. This is explained by the fact that some patients in clinical remission do not have an absence of disease activity, but rather exhibit a low level of inflammation that is not always easily detectable by clinical examination or reflected in laboratory results. The DAS 28 (Disease Activity Score 28 joints) is the most calculated score used in daily practice. This composite score includes objective, subjective and biological data. Other scores exist but are less used: the SDAI (Simple Disease Activity Index), the CDAI (Clinical Disease Activity Index), and the Boolean ACR/EULAR remission criteria. All these composite indices differ when considering remission according to the cut-off used. Indeed, in

the same group of RA patients, the number of those in remission according to DAS28 was higher compared to other remission scores such as SDAI.[3,4] Thus, DAS28 may not be considered as the most suitable to diagnose remission.

Thanks to the recent technical advances, musculoskeletal ultrasound of the joints is now playing an increasingly important role in the quantification of synovitis and provides us with important information for the diagnosis, the monitoring, and the management of RA.[5] The integration of this tool as an extension to clinical and biological data may be interesting to assess remission.[6] In that regard, we conducted the present study to investigate the validity of different RA disease activity scores to assess remission using the US as the reference.

Methods

Study design

This is an analytic, diagnostic monocentric study carried out in our Rheumatology department (Mongi Slim Hospital- Tunis- Tunisia) for ten months.

Patients and controls

Thirty patients with established RA, meeting the criteria of ACR 1987 and in remission according to the EULAR definition (DAS28 $\leq$2.6) were included.[7] Inclusion criteria were RA evolving for more than six months, age at the time of diagnosis greater than 16 years, and the state of remission (DAS28$\leq$2.6) diagnosed for at least 3 months. Exclusion criteria were: Patients who had a therapeutic adjustment, a flare disease, or a joint steroid injection three months prior to the study date. A control group (active-RA group) was considered to compare the validity of the various criteria for remission. It encompasses 37 patients with active established RA (DAS28 > 3.2).

Written consent was obtained from the participants. This study was conducted in accordance with the ethical principles of the declaration of Helsinki and approved by the Human Research Ethics Committee at Mongi Slim Hospital.

Data collected

At inclusion, clinical data were recorded including the age of onset of the disease, the duration of the morning stiffness, the number of night awakenings, visual analogic scale (VAS) of pain, patient and physician global assessment (GPA and PhGA). The tender and swollen joints count

(TJC and SJC) over 66 joints were assessed by the same physician who performed the investigation.

Laboratory markers including C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) levels were performed the same day. Immunologic assessment of Rheumatoid Factor (RF), the anti-citrullinated peptide antibodies (anti-CCP), and the anti-nuclear antibodies (ANA) was collected from the recorded data. The functional impact of the disease was assessed using the Health Assessment Questionnaire (HAQ).

Remission definitions

DAS28 is a composite RA activity score including TJC, SJC, GPA as well as the levels of ESR and CRP [7]. EULAR cut-off for disease activity was used, the study group had a DAS28 ≤2.6, and the control group a DAS28 > 3.2.

Other established scores considered in our study were: the SDAI (Simple Disease Activity Index), the CDAI (Clinical Disease Activity Index), and the Boolean ACR/EULAR remission criteria.[8-10]

The CDAI includes only clinical parameters: TJC, SJC, GPA, and PhGA. The SDAI includes all the latter plus the CRP levels. Remission cut-offs considered were: CDAI≤ 2.8 or SDAI≤ 3.3 or the Boolean ACR/EULAR remission criteria including TJC≤ 1, SJC≤ 1, CRP≤ 10mg/l, and GPA≤ 10.[11]

Ultrasound assessment

The US of the hands and the wrists was performed for each patient with a delay not exceeding 30 minutes after the clinical examination and the biological sampling. The US examination was performed by a rheumatologist expert in the musculoskeletal US with at least 10 years of experience. The operator was blinded to the study group and all other study findings. The equipment used was Esaote MyLAb 60 with a 6-18 MHz linear array probe. When using Power Doppler (PD), the pulse repetition frequency was adjusted at 500-750 Hz and the receiver gain was adjusted to eliminate the artifact.

Overall, 22 joints were scanned per patient: wrists, metacarpophalangeal joints (MCP), and proximal interphalangeal joints (PIP) bilaterally. Wrists and MCP were studied on the dorsal

side and PIP on their palmar side. The semi-quantitative scale of Szkudlarek was used in Grey-scale (GS) imaging evaluation for synovial hypertrophy (SH) and in Power Doppler (PD).[11]

The sum of grades obtained for each joint and each US mode was established such it was ranging from 0 to 66 for GS and DP.

We choose to not include ultrasound detection of erosions in this study as erosions primarily reflect cumulative lesions related to previous history rather than ongoing inflammation.

Validity of various remission scores

In order to study the validity of the various criteria, we considered the absence of Doppler signal on the US as the gold standard to define US remission. Sensitivity, specificity, positive (VPP), and negative predictive values (VPN) were calculated and compared between the different remission scores using US remission as reference. Considering US remission, a new threshold for quantitative scores (DAS28, CDAI, SDAI) was assessed using ROC curves. Then, the validity of each score was calculated using new values.

Concordance between remission scores

We assessed the concordance between DAS28 and the other RA activity assessment scores (CDAI, SDAI, ACR/EULAR remission) based on the kappa coefficient using US assessment as reference.

Statistical analyses

The data was transcribed using Excel and analyzed using the SPSS version 12.0 for Windows. We calculated simple frequencies and relative frequencies (percentages) for qualitative variables. We calculated averages, standard deviations and determined the extent (extreme values - minimum and maximum) for quantitative variables. Comparisons of two independent series averages were made using the Mann and Whitney non-parametric test. The independent series percentage comparisons were made by Pearson's Chi-2 test. Comparisons of two percentages on paired series were made by the Mac Nemar test. The links between the two quantitative variables were studied by spearman's rank correlation coefficient. The differences were found to be significant for a coefficient of meaning $p<0.05$. The agreement between two qualitative variables was measured by Cohen's Kappa coefficient. The thresholds for interpreting the kappa coefficient according to Landis and Koch were as follow k of 0–0.20

were considered poor, 0.20–0.40 fair, 0.40–0.60 moderate, 0.60–0.80 good, and 0.80–1 excellent.

Results

Overall, 67 patients with RA were included in the study. The study group (30 patients) were in remission according to DAS28 for a mean period of 16 months [3-72 months]. Half patients (50%) were under corticosteroids with an average dosage of 3.75 mg/day [5-10 mg/day]. Conventional disease-modifying anti-rheumatic drugs were prescribed alone in 80% and biotherapies in 20% of patients. The study group and the control group were comparable for demographic data. In the study group, rheumatoid factor and Anti-cyclic citrullinated peptide antibodies positivity were found in 60% and 66% of patients respectively. Antinuclear antibodies were available in 23 patients and positive in 10% of them with a mean titer of 1/160 [1/80-1/320].

In the active RA group (37 patients), Rheumatoid factor and Anti-cyclic citrullinated peptide antibodies positivity were positive in 79,8% and 73,6% of patients respectively. Antinuclear antibodies were positive in 6% of cases.

The comparison of different parameters between both groups was summarized in Table 1.

Ultrasonographic findings

Study group

Among the 660 joints studied, SH was detected in 14% of joints and PD signals in 7% of them. The most affected joints were the wrists. When considering the patient scale, synovitis was present in 80% of patients and PD in 57% of them (Figure 1).

Active RA group:

Among the 814 joints studied in US, SH was found in 44%, and PD in 36% of joints with a predilection for the wrists. Considering the patient scale, all of them had SH with at least one vascularized joint.

When comparing the two groups, a significant difference was noted both in GS and PD mode. A grade 0 was more frequent in the study group and a grade 3 was more frequent in the active

RA group in both modes. The Comparison of US grades between the two groups is represented in Table 2.

Validity of the different disease activity scores

We assessed the validity of different remission criteria by considering as gold standard the absence of any Doppler signals on ultrasound to define "real remission".

The absence of Doppler signals was found in 13 patients in remission and in one patient in the active-RA group. The DAS28 was the most sensitive (93%) and the most specific (68%). The validity of the different disease activity scores was resumed in Table 3. When considering the state of "real remission", the thresholds that corresponded to the best couple sensitivity-specificity were 3.2 for DAS28, 8 for CDAI and 6.5 for SDAI. The validity of each score using new limits according to ROC curves was represented in Table 4.

Correlation between the different disease activity scores and Ultrasonographic findings in the study group

In GS, synovitis was detected in 80%, 81%, 79%, and 78% using DAS28, CDAI, SDAI, and ACR/EULAR remission criteria respectively. In PD, vascularized synovitis was present in 57%, 58%, 53%, and 64% considering remission in DAS28, CDAI, SDAI, and ACR/EULAR remission criteria respectively. There was no significant correlation between any remission criteria used and US findings either in GS or in PD (Table 5).

Concordance of the different RA activity scores for the assessment of remission

Among patients in remission according to DAS28, twenty-six patients (87%) were in remission according to CDAI, nineteen patients (63%) were in remission according to SDAI and fourteen (47%) were in remission according to ACR/EULAR criteria. The agreement between DAS28 remission and CDAI was excellent (k=0.88), it was good between DAS28 and SDAI (k=0.66) and medium between DAS28 and ACR/EULAR remission criteria (k=0.47).

Discussion

To our knowledge, this is the first study that investigated the validity of four different clinical remission scores in RA patients using the US remission as a gold standard.

In our study, DAS28 was the most sensitive score (93%), followed by SDAI (78%), CDAI (64%) and ACR/EULAR remission (36%). The DAS28 was also the most specific (68%), followed by CDAI (65%), then SDAI (63%) and finally ACR/EULAR criteria (59%). In previous studies, only one study assessed the validity of SDAI in RA patients compared to the US. In that study, Balsa et al showed that, when the cut-off was set to 5, the sensitivity of SDAI was 65.5% and the specificity was 55% [12]. The specificity of this score was 74.4% when the cut-off was set to 3.3.[12] The authors concluded that an SDAI ≤ 3.3 seemed to be a more specific criterion of true remission aimed by the different therapeutic strategies than DAS28. Indeed, when the DAS28 score was used, a patient could be diagnosed in remission even when he has up to five swollen joints. However, the definition is more stringent with SDAI allowing the existence of either two painful or swollen joints, or one painful joint and one swollen joint.[13]

However, based on our results, we concluded that the DAS28 was more specific than the SDAI and therefore even better adopted to assess true remission. Interestingly, CDAI; which includes only clinical parameters; was found to be more specific than SDAI to assess remission. We did not found any previous study encompassing these findings.

Among the multitude of definitions and scores proposed to assess remission, we based our study on four of them, which can be easily used in daily practice. DAS28 ≤ 2.6 was the inclusion criteria since it is the most used in daily practice. The concordance between the different RA remission scores compared with the DAS28 was excellent (0.88) for CDAI, good (0.66) for SDAI and medium (0.47) for ACR/EULAR remission. In the study of Hmamouchi et al, the agreement of the different scores calculated for patients in remission in the French cohort ESPOIR was medium between DAS28 and SDAI remission (0.54) and poor between DAS28 and ACR/EULAR remission (0.44).[14] In another study by Chandrashekara et al including 100 RA patients in remission, no agreement between DAS28 and ACR/EULAR was found (r = -0.16).[15] An overall good agreement between the different scores was noted in our study, the differences with other studies could be related to patient selection.

There is no consensus on the number of joints and sites to assess by the US to evaluate RA activity. Many scores have been proposed in order to evaluate remission by the US. Taking into account the conclusions of the various authors, we evaluated in our work 22 joints: the wrists, the MCP, and the PIP of both hands. In our study, 80 % of patients had synovitis in GS and 57 % had vascularized ones.

A certain heterogeneity was found in published studies, which could be attributed to a different methodology and remission criteria. However, all the studies agreed on the persistence of US activity in patients in remission despite the used score. According to a systematic review by Ben Abdelghani et al including 12 studies of RA in remission, synovitis was detected in 50.7% to 95% in GS, and in 14.7 % to 57.4% in PD.[16] The detection of this synovitis was particularly important as it is this infra clinical activity that was responsible for a low-noise evolution during remission.[17] Not to mention that the US scoring system used was Szkudlarek instead of the EULAR as our study was conducted before the validation of the EULAR score.

As SH can be seen in many other diseases and even in healthy subjects, we considered the real remission state in our work, the lack of any Doppler signal.

In our study, no correlation between the DAS28 score and US score was found neither in B mode nor in PD mode. Only one study assessed the link between DAS28 and US scores. According to Balsa et al, a positive correlation was observed between DAS28 and PD ($r = 0.17$; $p = 0.043$).[12] The differences between this study and ours are probably due to the used methodologies. First, the number of patients in remission included was different (30 vs 74). Also, inclusion criteria and cut-off values assessing remission were different. Finally, these differences could mainly be due to the number of joints evaluated in US.

The strength of our study was that we assessed remission scores that are easily used in current practice. Moreover, a control group was included to calculate the validity of the different RA activity scores.

However, our work suffered from some limitations. The Duration of remission set to 3 months at inclusion may be considered insufficient since we have demonstrated the persistence of US synovitis in these patients. In literature, the minimum duration of remission varied from 3 to 18 months.[18] When the remission was prolonged to 6 and 12 months, PD was observed in 47,1% and 12,4% of patients respectively.[19] Another limitation was that the performance of the US examination depended on the technical characteristics of the device but also on the operator. In our study, a single operator performed all the US scanning. It would be interesting to perform the US assessments on 2 separate occasions and having a second sonologist perform the US assessments for a better validity of our results. However, our operator was an expert in the US,

and good intra and inter-observer reproducibility of the PD had been confirmed by several studies making its use by a single operator reliable. Another limitation concerns corticosteroids' use in the remission group. However, the majority of them were treated with low dosages (<7.5 mg/day) and were in remission for 16 months. Finally, we had chosen to consider the absence of PD in the US as a state of "real remission".

Our choice was based on the literature results, which showed the evidence that subclinical disease (persistent PD signal in clinical remission) is predictive of acute flares in RA and even of future structural damage. It is a very stringent criterion. However, this choice could be discussed since, on one hand, there is no clear consensus of the definition of ultrasound remission until now.

On the other hand, the implementation of the US in everyday practice as well as in follow-up has been reconsidered these last years. Indeed, some authors do not currently support the routine use of US assessment as part of an enhanced Treat-to-Target strategy recommended by EULAR.[20-22] Based on the results of the ARCTIC trial US tight control strategy did not show additional effect compared to the conventional tight control strategy.[22] The results of the TaSER study are in line with these findings. Indeed, aiming a total power Doppler joint count ≤1 as part of the US Treat-to-target strategy led to more intensive treatment with no better clinical or imaging outcomes when compared to the DAS28-driven strategy (DAS28 <3.2).[23] Indeed, raising the level of requirement in treating RA using the US as a reference did not augur well with the Treat to Budget concept. More studies are needed to assess the role of the US in evaluating disease activity and tailoring treatment in patients with RA.[22]

Conclusion

DAS28 followed by CDAI seemed to be the most specific scores to assess remission in RA since they are the closest to the concept of absence of inflammatory activity compared to other composite scores when considering true remission as the absence of PD signals in the US. We believe that these findings could be the basis for further research with a larger sample to draw effective conclusions.

Authors' Contribution

SM, YM, KO, SK, SC and LZ conceptualized and designed the study. SM and YM collected the data. KA, AF, MS, LS, KO, SK, SC, KS, LZ and AL analyzed and interpreted the data. KS performed the statistical analysis. YM performed the literature review and drafted the manuscript. SM edited the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

All authors do not declare any conflicts of interest in this work.

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Table 1: Demographic and clinical characteristics of patients and control group

Variable	Patients (n=30)	Control (n=37)	p
Age	48 ± 8,98 [33-67]	52.4 ± 10,3 [30-70]	0.38
Sex ratio (M/F)	0.20	0.15	0.5
Disease duration,years	8 ± 4,9 [1-23]	10 [0,5-38]	0.12
Night awakenings(mean)	1 [0-1]	1.23 [0-4]	**0.001**
Morning stiffness(minutes)	2 [0-30]	37.7 [0-240]	**0.001**
Tender joint count (0-28)	0 [0-1]	7 [0-27]	**0.001**
Swollen joint count (0-28)	0.3 [0-9]	6 [0-17]	**0.001**
VAS pain (0-100)	6 [0-10]	57 [10-100]	**0.012**
GPA (0-100)	3 [0-5]	5 [20-100]	**0.025**
ESR (mm/H)	16.7 ± 10,4 [2-40]	46 ± 25 [15-110]	**0.001**
CRP (mg/l)	3.1 ± 3,7 [0-19]	16.8 ± 15 [5-59]	**0.005**
DAS-28	2.03 [1,1-2,6]	5.2 [3,11-8,6]	**0.001**
HAQ	0.12 [0-1]	1.7 [0-2,62]	**0.001**

VAS : Visual Analogue Scale, GPA : Patient Global Assessment, CRP : C-Reactive Protein, RF ;Reumatoid Factor, ACPA : Anti-Citrullinated Peptide Antibodies, DAS-28 : Disease Activity Score, HAQ :Health Assessment Questionnaire

Table 2: Comparison of ultrasound grades between the study and the control group

		Study group (n=660)	Control group (n=814)	p
GS	**Grade 0 n,(%)**	571 (86)	460 (56)	**0.001**
	Grade 1 n,(%)	52 (8)	146 (18)	**0.001**

	Grade 2 n,(%)	31 (5)	154 (19)	**0.001**
	Grade 3 n,(%)	6 (1)	56 (7)	**0.001**
PD	**Grade 0 n,(%)**	616 (93)	518 (64)	**0.001**
	Grade 1 n,(%)	17 (3)	89 (11)	**0.001**
	Grade 2 n,(%)	17 (3)	114 (14)	**0.001**
	Grade 3 n,(%)	10 (0.1)	93 (11)	**0.001**

GS: Grey Scale, PD: Power Doppler

Table 3: Reliability of the different scores of remission in the study group

Remission score	Sensitivity	Specificity	PPV	NPV
DAS28 (%)	**93**	**68**	43	97
CDAI (%)	92	65	37	97
SDAI (%)	90	63	33	97
ACR/EULAR (%)	83	59	17	97

DAS28: Disease activity score 28 joints, CDAI: clinical disease activity index, SDAI: simplified disease activity index, ACR/EULAR: American college of rheumatology/ European league against rheumatism, PPV: positive predictive value, NPV: negative predictive value.

Table 4: Validity of the different scores of remission after ROC curve thresholds in the study group

Remission score (new thresholds)	**Sensitivity**	**Specificity**	**p**
DAS28=3,2 (%)	100	65,4	0,0001
CDAI=8 (%)	100	79,1	0,0001
SDAI=6,5 (%)	85,7	79,2	0,0001

DAS28: Disease activity score 28 joints, CDAI: clinical disease activity index, SDAI: simplified disease activity index

Table 5: Correlation between remission scores and ultrasonography scores in the study group

	Grey scale			**Power Doppler**		
	Mean score	**correlation r**	**p**	**Mean score**	**Correlation r**	**P**
DAS28	4.4	-0.209	0.268	2.7	-0.258	0.169
CDAI	4.5	0.104	0.319	2.6	0.251	0.217
SDAI	3.9	0.990	0.687	2.3	-0.036	0.884
ACR/EULAR	5.8	-	-	3.9	-	-

DAS28: Disease activity score 28 joints, CDAI: clinical disease activity index, SDAI: simplified disease, ACR/EULAR: American college of rheumatology/ European league against rheumatism. activity index

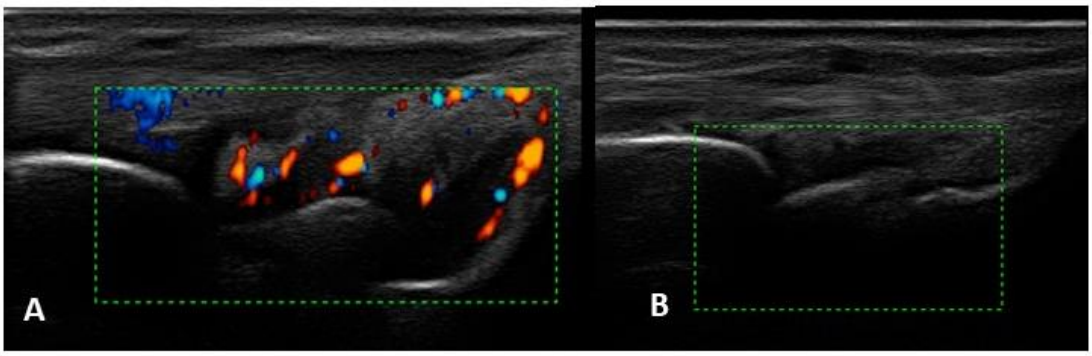

Figure 1: Ultrasound in clinical remission: power Doppler mode (A): persistent PD, (B): PD signal abolished.