

Comparable Clinical and Radiographic Outcomes among DAS28-ESR-based Remission Criteria and SDAI, CDAI, and ACR/EULAR Boolean definitions in patients with Established Rheumatoid Arthritis in Clinical Practice. Observational Study of 5 years of Follow-Up

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Abstract

Objective

To compare long-term clinical and radiographic outcomes among five sets of remission criteria [four clinical and one Ultrasound (US)-based] in a cohort of RA patients in a clinical care setting.

Methods

RA patients in remission (DAS28-ESR <2.6) were selected. Hand US assessments were performed, and serum levels of inflammation/angiogenesis biomarkers were determined at baseline. Changes in baseline treatment and radiographic progression, defined as the variation in the modified Sharp van der Heijde score (mSHS) at 5 years, were analyzed. To define remission, five different concepts were used, as follows: DAS28-ESR<2.6, SDAI<3.3, CDAI<2.8, Boolean criteria and score Power Doppler (PD)=0.

Results

Eighty-seven patients with DAS28-ESR<2.6 were included. One third fulfilled SDAI (33.3%), CDAI (31%) and Boolean (35.6%) remission criteria and 25.3% had no PD signal in the US evaluation. 26 patients (29.9%) changed the therapy, ranging from 13.6% (PD remission) to 33.3% (CDAI remission) ($p=0.11$). Serum levels of ANG ($p=0.015$) and TNFa ($p=0.025$) were significantly lower in patients with Boolean remission, whereas IL-18 levels were significantly lower in those with PD remission ($p=0.049$). Patients without PD in the US assessment had significantly lower mSHS erosion progression ($p=0.014$) at 5 years.

Conclusions

Patients with established RA in DAS28-ESR remission had comparable clinical and radiographic outcomes than SDAI, CDAI and Boolean definitions in a clinical care setting. US remission remained as the closest to structural damage abrogation.

Introduction

The main goal in the treatment of rheumatoid arthritis (RA) is to suppress the inflammatory process and achieve remission. Remission may be defined as a state with no or, at least, low disease activity. Ideally, remission should be maintained to abrogate joint damage progression [1].

Several sets of remission criteria have been proposed. The original American Rheumatism Association (ARA) remission criteria are infrequently used today since all components of the criteria are not included in the current core set of variables [2]. A Disease Activity Score (DAS) less than 1.6 was found to correspond well to the ARA remission criteria and was proposed as a remission criterion. Later, DAS remission was modified by a 28-joint count to the DAS28-ESR less than 2.6 criterion, which has been widely accepted [3–4]. However, DAS28-ESR criterion has been criticized as being not stringent enough,

as many patients under DAS28-ESR remission can still have low levels of disease activity. Therefore, more stringent criteria have been developed, for example, the Simplified Disease Activity Index (SDAI) less than 3.3 remission criterion and the Disease Activity Index less than 2.8 remission criterion (CDAI), which lacks acute phase reactants [5]. Recently, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), have jointly proposed that remission in RA may be defined either according to the SDAI or to the new Boolean-based set of criteria [6]. The Boolean Criteria have been shown to perform well in clinical trials, but their utility in long-term observational studies remains to be demonstrated [6].

We have previously demonstrated that around 60% of RA patients in DAS28-ESR remission have Power Doppler (PD) signal [7]. This subclinical ultrasound (US) activity has been related to higher structural damage progression after 12 months of follow-up [8].

The aim of this study was to compare clinical and radiographic outcomes among four different clinical sets of remission criteria and one remission criteria based on imaging (US) in a cohort of established RA patients in a clinical setting with 5 years of follow-up.

Patients And Methods

Observational study. Consecutive patients from the Rheumatology Department (Hospital Clinic, Barcelona, Spain) meeting ACR/EULAR 2010 criteria for RA [9] in clinical remission (defined as DAS28-ESR < 2.6) for > 6 months assessed by two rheumatologists were included. Clinical, epidemiological and serological data were analyzed. An ultrasound assessment of hands was performed, and serum biomarkers of inflammation and angiogenesis were determined at baseline. Patients were followed up for 5 years. Clinical and radiological data (radiographs of hands and feet) were collected.

The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (HCB-2017-0562). Signed informed consent was obtained from all patients.

Definitions and Study Outcomes

Remission was defined using five different concepts; four clinical and one based on imaging (US), as follows: DAS28-ESR < 2.6, SDAI < 3.3, CDAI < 2.8, ACR/EULAR Boolean (i.e. TJC \leq 1 and SJC \leq 1 and CRP \leq 1 mg/dl and PGA \leq 10 on a visual analogue 0-100 scale), and US PD score = 0.

Treatment change was defined as the change in any DMARD therapy (including synthetic or biologic DMARD but not glucocorticoids), across the observational period of 5 years.

Radiographic progression was defined with both, quantitative, as the difference between the last and first reading, and a qualitative concept based on the small detectable change, as it is explained below.

The proportion of patients with treatment change and radiographic progression throughout 5 years was calculated and compared across the five sets of remission criteria.

Ultrasound assessment

All sonographic assessments were performed using high-sensitivity ultrasound equipment (Acuson Antares®, Siemens AG, Erlangen, Germany). Sonographic assessments were made using a frequency range from 8 to 12 MHz. We used the same protocol detailed in previous works [7–8].

Intra-rater agreement was 0.81 for Synovial Hypertrophy and 0.92 for PD. This index was calculated as the percentage of agreement between these scores at two time points.

Radiographic assessment

All patients underwent postero-anterior X-rays of the hands and feet at baseline and at 5 years. Radiographic changes were graded anonymously by 2 trained readers (JR and AC), according to the modified Sharp van der Heijde score (mSHS) [10]. Intra-observer and inter-observer reliability were considered moderate to good;

We analyzed radiographic progression using a double approach.

First, we quantitatively measured the radiographic progression as the difference between the final and baseline score using both the total mSHS and the erosion sub-index score.

Secondly, using a qualitative approach, radiographic progression was defined as the change in the mSHS at 5 years > 10.47 [mdc (minimum detectable change)]. Radiographic evidence of structural progression was defined as a variation in the mSHS greater than the mdc, which was calculated using the following formula [11]:

$$\text{mdc} = 2 \times \text{SD} ([\text{obs}^{\text{a}}_{\text{followup}} - \text{obs}^{\text{a}}_{\text{baseline}}] - [\text{obs}^{\text{b}}_{\text{followup}} - \text{obs}^{\text{b}}_{\text{baseline}}])$$

Once defined the value of mdc, the value for each patient was calculated. If this value was higher than mdc we considered this patient as progressor. Using the same formula, we calculated the radiographic erosion progression, finally defined as 6.98.

Finally, we also used a less stringent cut-off for defining radiographic (mSHS > 5 , 1 unit/year) and erosion progression (> 5 , 1 unit/year).

Quantification of biomarkers of inflammation/angiogenesis

Cytokines and angiogenic mediators were analyzed using Quantibody® Human Custom Array (RayBiotech, Norcross, GA, USA). Each sample was diluted 2-fold and prepared in quadruplicate. An Axon scanner 4000B with GenePix software was used to collect fluorescence intensities. Detection limits for cytokines are displayed on the manufacturer's website [RayBiotech [http://www.raybiotech.com]]. After sample dilution, the effect of Rheumatoid Factor (RF) on the final results was estimated to be around 1% [12].

Calprotectin serum levels were determined using an ELISA Test Kit [CALPROLAB Calprotectin ELISA (ALP) CALPRO AS, Norway] in accordance with the manufacturer's protocol. [13].

Statistical analysis

Categorical and quantitative variables were described as frequencies, percentage and mean \pm standard deviation (SD). Clinical and radiographic outcomes were compared among the five remission criteria sets in a direct head-to-head comparison by the non-parametric Mann-Whitney U test, T-student or X^2 test, as appropriate. Subsequently, we compared serum levels of biomarkers in a direct head-to-head comparison between the five groups using non-parametric tests. A value of $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS V. 20.0 (SPSS. Chicago, Illinois, USA).

Results

Eighty-seven patients were included. Eighty-five per cent of the patients were women. Mean age was 57 years (SD 12.2) and disease duration was 145 months (SD 113). Sixty-five (74.7%) and 71 patients (81.6%) were either RF or ACPA +, respectively. Twenty-seven patients (31%) were taking oral prednisone (all of them at doses of ≤ 5 mg/day), 73 (83.9%) conventional disease modifying antirheumatic drugs (csDMARDs) and 54 (62.1%) biological therapy. At baseline, 65 patients (74.7%) had PD signal (Table 1).

Table 1
Baseline characteristics.

	Total patients
	n = 87
Age (years), mean (SD)*	57.06 (12.26)
Male, n (%)	13 (14.9)
BMI, mean (SD)	25.44 (5.20)
Disease duration (months), mean (SD)	145.62 (113.03)
TJC, mean (SD)	0.13 (0.39)
SJC, mean (SD)	0.26 (0.67)
Patient GA, mean (SD)	21.84 (11.96)
Physician GA, mean (SD)	17.59 (9.99)
mHAQ, mean (SD)	0.224 (0.333)
ESR (mm/h), mean (SD)	12.22 (7.18)
CRP (mg/dL), mean (SD)	0.26 (0.39)
DAS28-ESR, mean (SD)	2.07 (0.45)
SDAI, mean (SD)	4.62 (2.19)
CDAI, mean (SD)	4.37 (2.22)
RF, n (%)	65 (74.7)
RF (IU), mean (SD)	191.75 (314.71)
ACPA, n (%)	71 (81.6)
ACPA titres (IU/ml), mean (SD)	609.67 (641.32)
PDN, n (%)	27 (31)
csDMARD, n (%)	73 (83.9)
bDMARD, n (%)	54 (62.1)

*Data are expressed as mean (standard deviation) or as percentage;

ACPA: anti-cyclic citrullinated peptide/protein antibody; bDMARD: biological Disease-Modifying antirheumatic drug; BMI: Body Mass Index; CDAI: Clinical Disease Activity Index; CRP: C-Reactive Protein; csDMARD: conventional synthetic Disease-Modifying antirheumatic drug; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; GA: Global Assessment; mHAQ: Modified Health Assessment Questionnaire; PDN: prednisone; PDUS: Power Doppler Ultrasound; RF: Rheumatoid Factor; TJC: tender joint count; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; SH: synovial hypertrophy.

	Total patients
	n = 87
PDUS (%)	65 (74.7)
*Data are expressed as mean (standard deviation) or as percentage;	
ACPA: anti-cyclic citrullinated peptide/protein antibody; bDMARD: biological Disease-Modifying antirheumatic drug; BMI: Body Mass Index; CDAI: Clinical Disease Activity Index; CRP: C-Reactive Protein; csDMARD: conventional synthetic Disease-Modifying antirheumatic drug; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; GA: Global Assessment; mHAQ: Modified Health Assessment Questionnaire; PDN: prednisone; PDUS: Power Doppler Ultrasound; RF: Rheumatoid Factor; TJC: tender joint count; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; SH: synovial hypertrophy.	

All patients fulfilled DAS28-ESR remission criterion (< 2.6) at baseline. One third of them also fulfilled SDAI (33.3%), CDAI (31%) and ACR/EULAR Boolean (35.6%) remission criteria and 22 patients (25.3%) had no PD signal in the US evaluation (Table 2).

Table 2
Rates of remission and baseline and clinical Follow-up at five years.

	Clinical Follow-up at 5 years					
	Baseline		Remission at 5 years		Change Treatment	
	n	%	n	%	n	%
DAS28-ESR Rem	87	100	59	67,8	26	29,9
SDAI Rem	29	33,3	16	18,4	9	31
CDAI Rem	27	31	15	17,2	9	33,3
Boolean Rem	31	35,6	15	17,2	10	32,3
PD Rem	22	25,2	No data		3	13,6
CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; PD: Power Doppler; Rem: Remission; SDAI: Simplified Disease Activity Index.						

Clinical Outcomes at 5 years

Twenty-six out of 87 patients (29.9%) changed the DMARDs (conventional synthetic or biological) therapy along the 5 years of follow-up. Only slight differences were found among patients in remission according to clinical criteria [DAS28-ESR (29.9%), SDAI (31%), CDAI (33.3%), Boolean (32.3%)]. Patients in PD remission had fewer changes of baseline therapy (13.6%) but statistical differences were not reached ($p = 0.11$) (Table 2).

Angiogenic and Inflammatory biomarkers

Serum levels of ANG ($p = 0.015$) and TNFa ($p = 0.025$) were significantly lower in patients in SDAI remission and IL18 serum levels were significantly lower in patients in PD remission ($p = 0.049$) (Fig. 1). No other remarkable differences were found in serum levels of angiogenic and inflammatory biomarkers across de five sets of remission criteria. Of remark, serum levels of inflammatory biomarkers such as calprotectin, IL-6 or IL17F were balanced across the five sets of remission criteria.

Radiographic Progression

Globally, radiographic progression was low in all groups, with a mean mSHS progression slightly above 1 unit per year. Patients in PD remission had the lowest mSHS progression across groups. Remarkably, we found that patients in PD remission had significantly lower mSHS erosion progression (mean 1.36, SD 1.94, $p = 0.014$) after 5 years (Fig. 2).

Using a qualitative approach [mSHS threshold of 10.47(mdc)], radiographic progression ranged from 4.5% of patients in PD remission to 14.8% of patients in CDAI remission. Erosion progression above 6.98 (mdc) ranged from 4.5% for patients in PD remission to 16.1% for patients in Boolean remission. No significant differences were found among them. When a less stringent cut-off was used for determining radiographic progression (> 5 , 1 unit/year), range raised to 47.1–61.3% for mSHS progression (p -value non-significant) and 4.5–38.7% for mSHS erosion progression ($p = 0.005$ for PD remission) (Table 3).

Table 3

Rates of radiographic progression at five years. mSHS and erosion subindex are shown. Two cut-offs were used: mdc and another less stringent (1 unit per year). * $p = 0.005$

	Radiographic Progression at 5 years							
	mSHS Progression				Erosion Progression			
	> 10.47 (mdc)		> 5		> 6.98 (mdc)		> 5	
	n	%	n	%	n	%	n	%
DAS28-ESR Rem	9	10,3	41	47,1	9	10,3	19	21,8
SDAI Rem	4	13,8	17	58,6	4	13,8	10	34,5
CDAI Rem	4	14,8	15	55,6	3	11,1	9	33,3
Boolean Rem	4	12,9	19	61,3	5	16,1	12	38,7
PD Rem	1	4,5	11	50	1	4,5	1	4,5*

CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; mdc: minimum detectable change; mSHS: modified Sharp van der Heijde Score; PD: Power Doppler; Rem: Remission; SDAI: Simplified Disease Activity Index.

Sustained Remission

After 12 months of follow-up, 57 patients (65%) maintained DAS28-ESR remission and 21 patients (58.3%) were in remission according to stricter criteria (either SDAI, CDAI or Boolean definitions). At the end of the follow-up, 59 patients (67.8%) and 9 patients (10.3%) continued in remission according to DAS28-ESR and stricter criteria, respectively.

Changes of baseline therapy and radiographic progression were numerically lower in patients with sustained remission either at 12 month or at 5 years (data not shown) although the reduced population hampered comparisons between groups.

Discussion

The advent of biologic agents has allowed to reach new and ambitious outcomes in RA. Consistently, the cornerstone of the Treat To Target recommendations was the definition of an achievable treatment target, i.e. remission or at least low-disease activity [1].

DAS28-ESR < 2.6 has been the definition most widely used for remission in clinical practice. However, it has been suggested that disease activity could still be present in patients fulfilling that criterion. New ACR/EULAR definitions are more stringent and fewer patients are classified as being in remission using these concepts. Accordingly, barely half of patients with DAS28-ESR < 2.6 fulfilled SDAI or ACR/EULAR Boolean remission criteria in clinical practice [14]. However, whether or not more stringent remission criteria provide better clinical and radiographic outcomes in the long term is still under debate. Selecting more stringent remission criteria implies, on one hand, fewer joint counts and less subclinical activity [15–16]. On the other hand, the more stringent is our target, the more we will step up the therapy to achieve the goal, with a subsequent higher risk of adverse events [17].

In this observational study of clinical practice, DAS28-ESR criterion identified remission three-fold as often as SDAI, CDAI, ACR/EULAR Boolean and PD remission criteria.

The number of patients classified in remission (27–31%) and the rate of change of therapy (31-33.3%) were not essentially different among SDAI, CDAI and Boolean criteria. Even radiographic progression, no matter the threshold used, was quite balanced among them. Therefore, ACR/EULAR remission definitions could be interchangeable, as it has been previously highlighted [18].

Remarkably, no significant differences were reached among SDAI, CDAI, Boolean criteria and DAS28-ESR criterion with regard to change of baseline therapy after 5 years of follow-up. Even radiographic progression was not substantially different. Previous studies also showed that the DAS28-ESR remission criterion had similar radiographic damage and disability than that seen with other criteria, and patient-reported outcomes were similar [19–20]. The global low level of radiographic progression, barely above one unit of mSHS per year, in part explained by the high use of biological therapy at baseline (60%), definitely influenced the low structural damage progression and hampered the comparison among groups. According to our results, patients in remission, whatever the concept used to define it, have no relevant radiological progression in the long-term.

The two main drawbacks of DAS28-ESR-based remission are, on one hand, the excessive weight in the formula for acute phase reactants, giving an advantage to IL-6-inhibiting agents [21]. In this particular case, indexes such as CDAI or RAPID-3, not taking into account acute phase reactants, should be of first election [22–23]. On the other hand, a substantial amount of subclinical inflammation persists in patients in DAS28-ESR remission [24]. It is important to highlight that clinical remission, no matter the definition employed, does not entirely correspond to imaging remission and some patients might experience structural damage progression [25–27]. However, very few patients of our cohort had significant radiographic progression as measured by mSHS (less than one unit per year), as it has been seen in previous studies [19].

In order to discern which remission criterion is closer to arrest structural damage in our patients with established RA, we took different thresholds for radiographic progression. We observed that PD remission was related to better radiographic outcomes than exclusively clinical remission definitions, something already known for early rheumatoid arthritis [28]. Ideally, achieving US remission and the complete abrogation of subclinical activity should be the ultimate goal for our RA patients. However, recent data from TASER [17], ARTIC [29] and IMAGINE-RA [30] trials showed that specifically targeting subclinical inflammation did not yield better clinical outcomes. This target could imply a risk of overtreatment, with a higher use of biological therapy and more adverse events. No clear explanation exists for this. Maybe, Treat to Target strategies are not effective for treating subclinical inflammation or, alternatively, persistent subclinical synovitis does not imply worse clinical outcomes in the long-term. We previously have reported that, despite half of patients in remission still have US subclinical activity, the rate of radiographic progression was relatively low (10%) and, most probably, clinically irrelevant [31]. Our results suggest that targeting remission whatever the concept selected, should be appropriate to achieve good clinical and radiological outcomes in a clinical care setting for patients with established RA.

According to our results, DAS28-ESR is not inferior to more stringent remission concepts in a clinical care setting after a long follow-up. SDAI, CDAI and ACR/EULAR Boolean criteria are definitely more appropriate for clinical trials, where comorbidities are specifically avoided, and patients' assessments and acute phase reactants are related exclusively to RA and not to other extra-conditions seen in a real world-setting [20]. For routine clinical practice, DAS28-ESR could be acceptable, achievable in a high percentage of patients and more suitable for "real" patients with comorbidities. Similar levels of serum calprotectin found across the five sets of remission, a biomarker strongly related to subclinical inflammation and radiological progression [13, 32], reinforces the idea of comparable outcomes for all remission definitions in the long-term. US remission yielded significantly better radiographic outcomes than clinical criteria. Due to the uncertain value of structural damage associated with subclinical synovitis, this should not be an important limitation for the use of non-imaging criteria in clinical practice, especially in established RA.

If aiming for a state closer to normality (true remission), a concept of multi-dimensional remission (MDR) should be used, involving the achievement of different depths of remission, using clinical, imaging and additional serological, immunological or histological parameters [33]. MDR has been shown to be related

to better patient-reported outcomes, although prospective data is necessary to definitely address this issue.

This study has some limitations. The sample size was not big, and patient's data was retrospectively collected from medical records, although the long-term follow-up and the objective outcomes selected, such as change of therapy and radiographic progression partially outweigh these drawbacks. Second, patients' global assessment but neither pain assessment nor HAQ were recorded along the follow-up, since these two patient-related outcomes are not included in our routine monitoring of RA in clinical practice. In addition, since the current study was conducted in a clinical setting, we did not use a pre-established treatment protocol. Finally, few data on sustained remission was collected due to the reduced number of patients. This concept of persistent remission could be of relevance, since the continual fulfillment of any remission criteria has been strongly effective in preventing progression of functional disability [34].

Conclusions

DAS28-ESR remission criterion, in routine clinical setting, provided similar outcomes in the long-term than most recent and stringent clinical criteria for patients with established RA. Therefore, taking DAS28-ESR < 2.6 as our final target in a tight control strategy, could be appropriate for most patients in clinical practice and might also avoid overtreatment.

List Of Abbreviations

ACPA, Anti-Citrullinated Peptide/Protein Antibodies; ACR, American College of Rheumatology; ANG, ANGIopietin; ARA, American Rheumatism Association; csDMARDs, conventional synthetic Disease-Modifying Antirheumatic Drugs CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARDs, disease-modifying antirheumatic drugs; ELISA, Enzyme-Linked ImmunoSorbent Assay; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; IL, interleukin; mdc, minimum detectable change; MDR, MultiDimensional Remission; MHz, MegaHertz; mSHS, modified Sharp van der Heyde Index; obs, observation; PD, Power Doppler; PGA, Patient Global Assessment; RA, Rheumatoid Arthritis; RAPID-3, Routine Assessment of Patient Index Data 3; RF, Rheumatoid Factor; SD, Standard Deviation; SDAI, Simplified Disease Activity Index; SH, Synovial Hypertrophy; SJC, Swollen Joint Count; TJC, Tender Joint Count; TNF-a, Tumor Necrosis Factor Alpha; US, Ultrasound.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (HCB-2017-0562). Signed informed consent was obtained from all patients.

Consent for publication

Signed consent for publication was obtained from all patients.

Availability of data and consent to participate

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JR and JDC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. JR, JDC and RS were responsible for the study design. JR, JIM, VRE, RCM, AP, RC, AC, JGP performed data acquisition, analysis, interpretation, and final approval of the manuscript. Manuscript preparation was by JR, JDC and RS. All authors read and approved the final manuscript.

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Figures

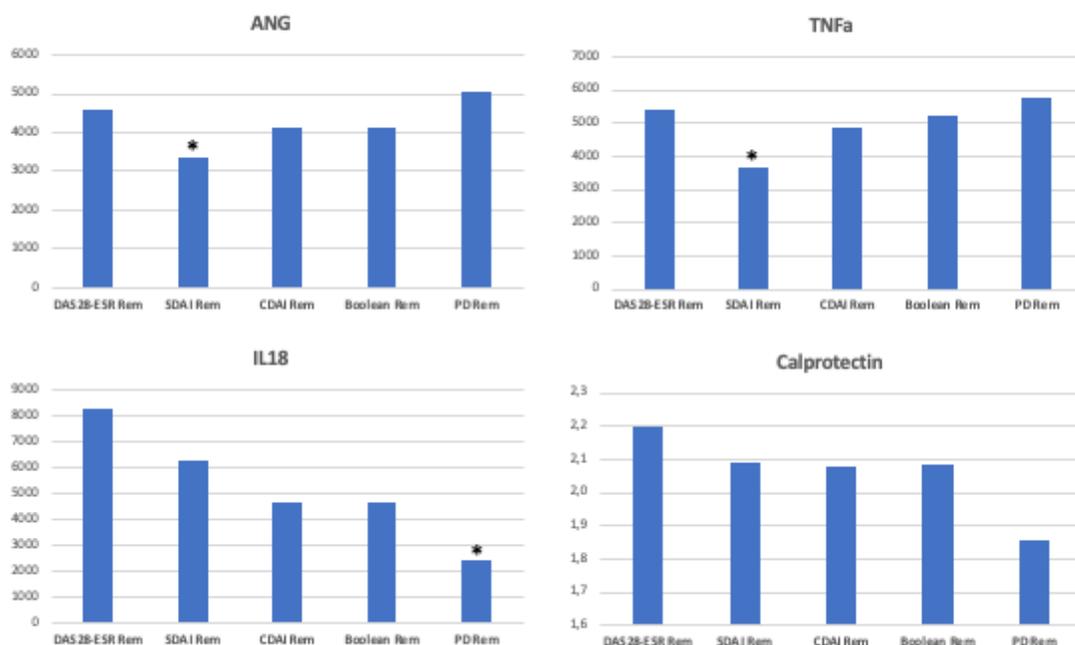


Figure 1

Serum levels of biomarkers among five sets of remission criteria. ANG: Angiopoietin; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; IL: Interleukin; mdc: minimum detectable change; mSHS: modified Sharp van der Heijde Score; PD: Power Doppler; Rem: Remission; SDAI: Simplified Disease Activity Index; TNFa: tumor necrosis factor-alpha. Serum levels of cytokines are shown in pg/ml. *p<0.05

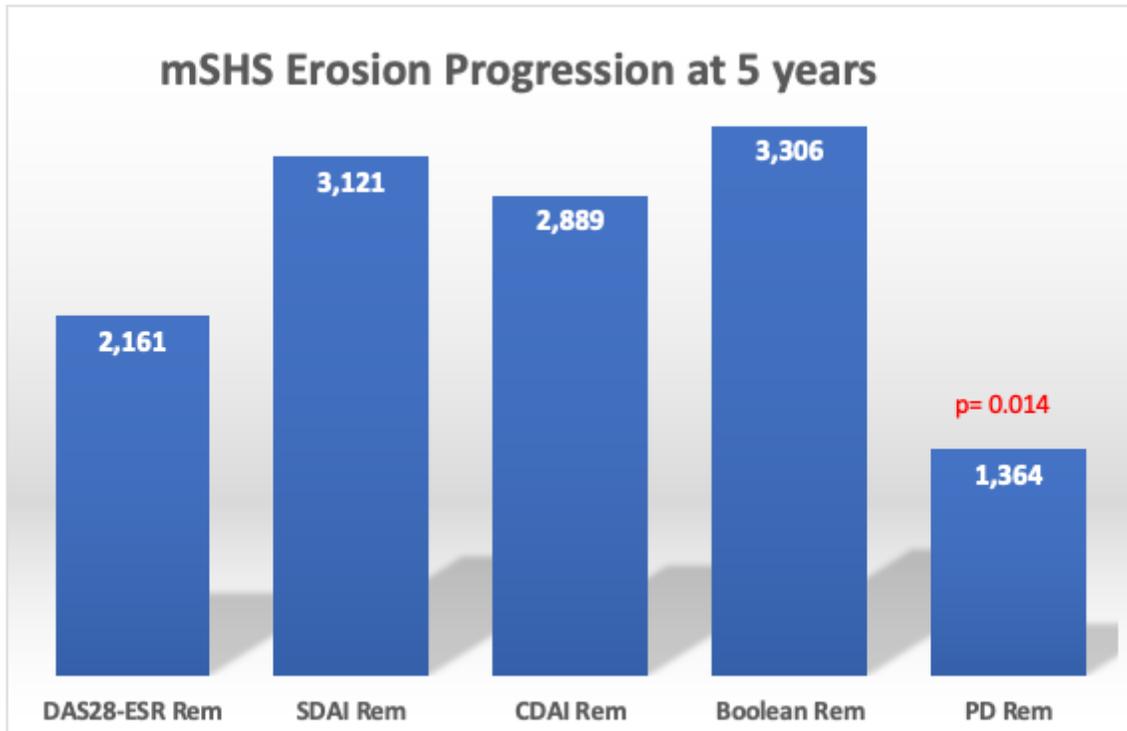


Figure 2

Serum levels of biomarkers among five sets of remission criteria. ANG: Angiopoietin; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; IL: Interleukin; mdc: minimum detectable change; mSHS: modified Sharp van der Heijde Score; PD: Power Doppler; Rem: Remission; SDAI: Simplified Disease Activity Index; TNFa: tumor necrosis factor-alpha. Serum levels of cytokines are shown in pg/ml. *p<0.05