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Original Article

The new ACR/EULAR criteria for rheumatoid arthritis can identify patients with same disease activity but less damage by ultrasound

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Abstract

Objective: We aimed to compare the ultrasound findings of patients fulfilling the 1987 ACR [OLD-rheumatoid arthritis (RA)] and the new ACR/EULAR (NEW-RA) classification criteria to examine the impact of the new criteria on disease characteristics, particularly disease duration.

Material and Methods: A total of 2730 hands, wrists, elbows, knees, ankles, and foot joints of 105 consecutive patients with inflammatory arthritis, i.e., 82 patients fulfilling the RA criteria (60 patients, OLD-RA; 22 patients, NEW-RA alone) and 23 patients with undifferentiated arthritis, were scanned using ultrasound. Synovitis, erosions, and power Doppler (PD) findings were scored using a scale of 0-3 and scores form each joint were added up to calculate synovitis, PD and erosion scores for each patient.

Results: OLD-RA and NEW-RA patients had similar swollen joint count, tender joint count, acute-phase response, patient global, and disease activity assessment 28 scores. The disease duration was longer in OLD-RA patients [30 (3-179) months] than in NEW-RA patients [16 (0-45) months; p=0.009]. Both the groups had similar synovitis and PD scores, whereas erosion scores were higher in OLD-RA patients than in NEW-RA patients (p=0.009). Patients with undifferentiated arthritis were older than those with RA and had fewer swollen joints than NEW-RA patients [0 (0-4) vs. 2 (0-9); p=0.017]. All other disease activity parameters were similar in both NEW-RA and OLD-RA patients. Both the synovitis (p=0.006) and erosion (p=0.007) scores were lower in patients with undifferentiated arthritis than in OLD-RA patients, despite the scores being similar to those in NEW-RA patients.

Conclusion: The new ACR/EULAR RA criteria enabled the classification of patients with similar disease activity (by clinical assessment and ultrasound) but with less damage. A similar disease activity should ensure suitability for an intervention, and a shorter duration and less damage should improve the outcome with patient benefit.

Keywords: Rheumatoid arthritis, ultrasound, doppler

Introduction

In recent years, the outcome of rheumatoid arthritis (RA) therapy has dramatically improved mainly because of new therapeutic developments along with advances in imaging. Remission is now not only achievable but also strongly recommended as a treatment target (1). The extensive use of sensitive imaging tools such as ultrasonography and magnetic resonance imaging has enabled earlier diagnosis and better understanding of the disease pathogenesis.

Until 2010, the 1987 ACR classification criteria for RA were used in clinical trials and for treatment recommendations (2). However, this set of criteria was criticized for including features of late disease, e.g., rheumatoid nodules, and signs of damage such as erosions on X-ray. This is particularly important as evidence shows that earlier treatment produces better patient outcomes and response rates (3-4). Therefore, erosions should not be provided as a feature of RA but rather be viewed as a consequence of failure of therapy to suppress inflammation. To overcome this limitation, the ACR/EULAR group published new classification criteria in 2010 with the aim of achieving an earlier diagnosis and therapy (5). These new criteria allowed weighting according to the number of joints involved, acute-phase reactants, seropositivity, and disease duration. The requirement of the presence of erosions was also excluded. Various studies have compared both the 2010 ACR/EULAR and 1987 ACR classification criteria by considering different standards as references. Both the criteria have been tested in cohorts from both clinical trials and routine practice, and a recent meta-analysis reviewed the performance of the new criteria (6). In this meta-analysis, when patients with other diagnoses were excluded, the new criteria demonstrated an almost 21% higher sensitivity then

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that of the old criteria, with a specificity of 16%. It has also been demonstrated that patients fulfilling the 1987 ACR criteria are more likely to have radiographic damage than those fulfilling the 2010 ACR/EULAR RA classification criteria (7). To date, it is not known whether there are any differences in terms of the burden of inflammation when the comparison is made using a more sensitive tool such as imaging.

Ultrasonography has been widely used in rheumatology for more than a decade for earlier diagnosis and more accurate assessments because it is more sensitive than physical examination for detecting synovitis (8). In this study, we aimed to compare the ultrasound (US) findings of patients fulfilling each criterion to examine the impact of the 2010 ACR/EULAR RA classification criteria on disease characteristic, particularly in patients with different disease duration.

Material and Methods

Clinical assessment for diagnosis and disease status

IACON is an ongoing early arthritis cohort in Leeds Musculoskeletal Biomedical Research Unit. The study was approved by the local ethics committee, and all patients provided consent before participating in the study. For this study, the first 105 consecutive patients from that the IACON cohort were recruited. All the patients underwent a clinical assessment, including the history of their disease and their current disease activity. Disease activity was assessed by DAS28, and their functional status was assessed by HAQ. Their rheumatoid factor (RF) and anti-CCP status were recorded from their records. Patients were then classified using a stepwise approach:

First step: Did they have RA according to the 2010 ACR/EULAR RA classification criteria (NEW-RA)?

Second step: If not, did they have RA according to the 1987 ACR classification criteria (therefore not fulfilling the 2010 ACR/EULAR RA classification criteria) (OLD-RA)?

Patients not fulfilling any of the two criteria were classified as undifferentiated arthritis.

Ultrasound assessments

Within 1 week of their clinical assessment, all patients underwent an US scan. The sonographer was blinded to their clinical assessment and their diagnosis. All US assessments were performed in a darkened room using a Logiq E9 machine (General Electric; Wauwatosa, Wisconsin USA) and a linear probe at 9-14 MHz. A total of 2730 joints were scanned using US, i.e., 26 joints per patient. The joints examined were the wrists, second and third metacarpophalangeal and proximal interphalangeal joints, elbows, knees, ankles, and 1st-5th metatarsophalangeal joints bilaterally.

To scan the wrists and hands, the hands were in full extension. Dorsal scan was performed for gray-scale synovitis and power Doppler (PD) assessments; additionally, the lateral and medial sides were scanned for erosions. Both anterior and posterior scans were performed for the elbows (in full extension for anterior scans and in 90 degrees of flexion for posterior scans). Knees were semiflexed to 30 degrees for gray-scale synovitis but were flexed in the neutral position to assess the Doppler signal. To scan the tibiotalar and metatarsophalangeal joints, the ankles were in the plantar flexion with the feet stepping on the examination bed. The metatarsophalangeal joints were scanned from the dorsal aspect for synovitis, in addition to the lateral scans for assessing erosions.

Synovitis, erosions, and PD findings were defined according to the definitions developed by the OMERACT US taskforce (9). A semiquantitative scoring system was used. Gray-scale synovitis was scored between 0 and 3, with 0 being none, 1 being mild, 2 being moderate, and 3 being marked synovial thickening. For scoring PD signal, the following scoring was used: score 0, no Doppler signal; score 1, one or two vessels (including one confluent vessel) for small joints and two or three signals for large joints (including two confluent signals); score 2, PD signal more than score 1 but <50% of the area; score 3, PD signal covering >50% of the gray-scale synovitis. Erosions were scored as 0 if there was no erosion, scored 1 if the maximum diameter of the erosion was <2 mm, scored as 2 if the diameter was ≥2 but <4 mm, and scored as 4 if ≥4 mm (Figure 1a). Three types of US scores were calculated: gray-scale synovitis, PD scores, and erosions. Scores were calculated by adding each relevant score for each joint.

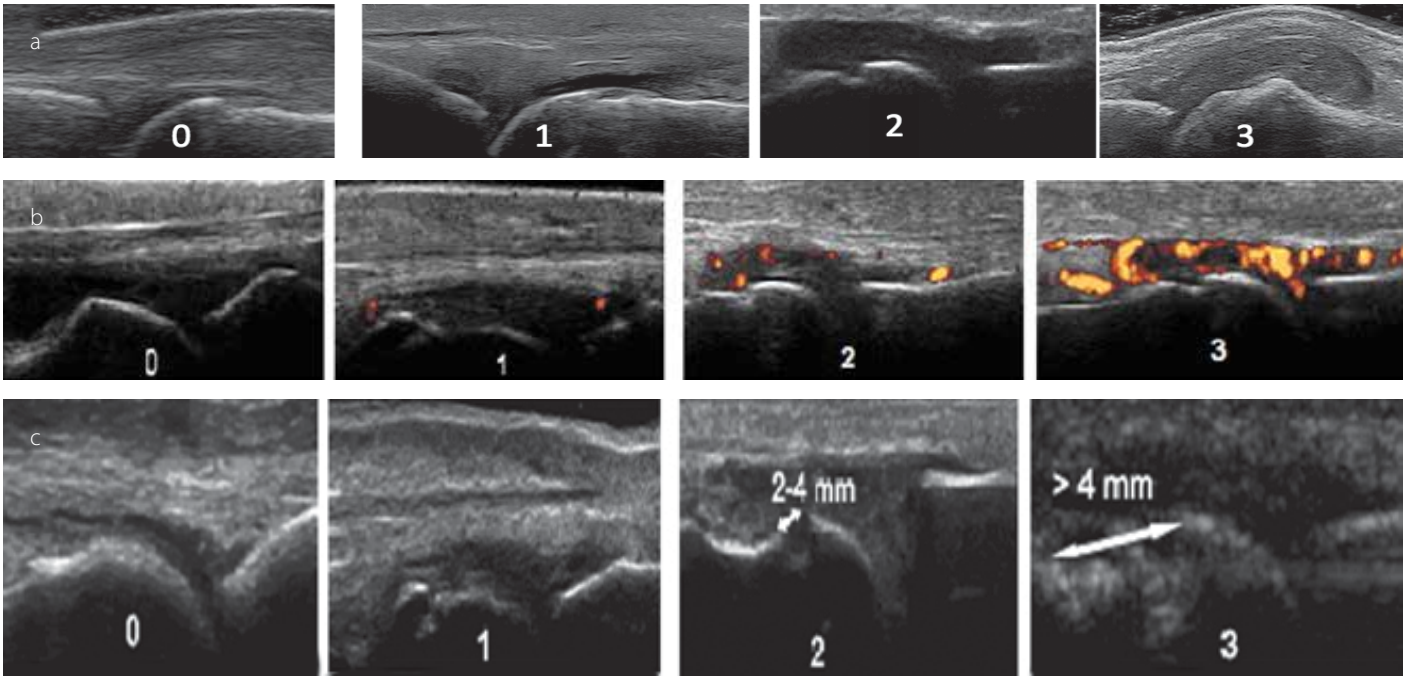

Figure 1. a-c. Semiquantitative scoring of synovial hypertrophy on gray-scale synovitis (a); Semiquantitative scoring of Doppler signals (b); Semiquantitative scoring of erosions (c)

Table 1. Baseline demographics and clinical disease activity parameters of the three groups

	OLD-RA (n=60)	NEW-RA (n=22)	Undifferentiated arthritis (n=23)
Age	48 (26-85)	51 (27-77)	67 (38-85)
Disease duration	30 (3-179)	16 (0-45)	21 (3-54)
Sex: no of females (%)	44 (73.3)	15 (68.2)	17 (70.9)
SJC	1 (0-20)	2 (0-9)	0 (0-4)
TJC	3 (0-24)	2 (0-12)	2 (0-10)
CRP	5.4 (0-157)	0 (0-34)	0 (0-166)
ESR	24 (0-126)	24 (0-63)	10 (0-304)
Pat global	19 (0-98)	26.5 (1-78)	18 (2-70)
DAS28	3.6 (0.01-7.68)	3.7 (0.97-6.23)	3.8 (0.5-5.4)
RF % *	68.3	64.3	17.6
Anti-CCP % #	70.2	71.4	28.6
HAQ	4 (0-19)	9 (0-16)	3 (0-15)

Numbers are given as median (range) unless mentioned otherwise.

SJC: wollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; Pat global: patient global score; DAS28: disease activity assessment 28; HAQ: health assessment questionnaire

Data were available in 72 patients for RF (*) and in 99 patients for anti-CCP(#).

Table 2. Ultrasound scores of three groups related to gray-scale synovitis, power Doppler (PD), and erosions. Numbers are given as median (range)

	Ultrasound scores		
	Synovitis	PD	Erosions
OLD-RA	19.5 (2-49)	0 (0-15)	4 (0-18)
NEW-RA	16.5 (2-30)	0 (0-6)	1 (0-10)
Undifferentiated arthritis	10 (0-35)	0 (0-5)	1 (0-9)

Synovitis scores: OLD-RA vs. UA: p=0.006; OLD-RA vs. NEW-RA and NEW-RA vs. UA: non-significant

Doppler scores: all pair comparisons are insignificant.

Erosion scores: OLD-RA vs. UA: p=0.007; OLD-RA vs. NEW-RA: p=0.009; and NEW-RA vs. UA: non-significant.

Statistics

Data are expressed either as frequencies or median (range). For comparison of the demographics, chi-square test was used for categorical variables. Continuous variables were compared using Kruskal-Wallis test for comparison of all groups, followed by Mann-Whitney U test for paired comparisons. Bonferroni correction for multiple testing was used, and the correction was set at $p<0.017$, calculated by dividing 0.05 by three groups. Statistical analysis was performed using the SPSS version 11.5 (SPSS Inc.; IL, Chicago, USA).

Results

Baseline demographics

There was a significant difference for age (p=0.003) and disease duration (p=0.02) among the groups using Kruskal-Wallis test. Paired comparisons showed that patients with OLD-RA and NEW-RA were of similar ages, whereas those with undifferentiated arthritis were older than those with OLD-RA (p=0.002) and NEW-RA (p=0.002) (Table 1). The sex distribution was similar across all groups. The disease duration was longer in OLD-RA [30 (3-179) months] than in NEW-RA [16 (0-45) months; p= 0.009] but statistically not different from patients with undifferentiated arthritis [21 (3-54) months]. A greater proportion of patients with OLD-RA and NEW-RA were RF and anti-CCP positive then those with undifferentiated arthritis (for RF: p= 0.001 and p=0.012 respectively) (for anti-CCP: p= 0.002 and p=0.013, respectively).

Clinical disease activity and functional assessment

All patient groups had similar swollen and tender joint counts, patient global assessments, ESR, and CRP levels, except patients with undifferentiated arthritis who had fewer swollen joints than NEW-RA patients (p=0.017) (Table 1). Compatibly, DAS28 scores were also similar among all three groups. RA patients according to NEW-RA had higher HAQ scores than the undifferentiated arthritis patients (p=0.003), but the difference between NEW-RA and OLD-RA was not significantly different after Bonferroni correction (p=0.048).

US scores for inflammation and damage

Both OLD-RA and NEW-RA groups had similar synovitis and PD scores.

The synovitis scores of patients with undifferentiated arthritis were lower than those of OLD-RA (p=0.006), despite being similar to those of NEW-RA (Table 2).

Erosion scores of the patients with OLD-RA were higher than those with NEW-RA (p=0.009).

The erosion scores (p=0.007) of patients with undifferentiated arthritis were lower than those with OLD-RA, despite being similar to those with NEW-RA.

Discussion

This US study showed that the 2010 ACR/EULAR classification criteria for RA enabled the classification of patients with similar disease activity but with less damage. The identification of patients at a disease stage with less damage should improve therapeutic outcomes.

In this study, similar disease activity, in terms of both clinical assessment and US findings, was observed independent of fulfilling either of the classification criteria. This is in contrast with that previously reported where patients who fulfilled only the 2010 criteria, but not the 1987 criteria, had fewer swollen joints and lower DAS28 scores (10-11). However, in the study by de Hair et al, the rates of RF and anti-CCP positivity were less in the group diagnosed according to the 2010 criteria, whereas the rates were similar in this study (11). The only significant demographic difference between the 1987 and 2010 criteria was the disease duration, which was longer for the 1987 criteria, as expected. The difference in the serology may partially explain the differences of disease burden in the NEW-RA group across different studies.

Compatible with our results, a study comparing histological findings of the synovium of patients, classified according to the 2010 ACR/EULAR vs. 1987 ACR classification criteria, found that cellular infiltrates (and the overexpression of VEGF and VCAM-1) and increased vascularity were indistinguishable in patients classified according to both the criteria (12). Thus, the main advantage of the new criteria is not its ability to detect milder disease but that it may be able to identify patients at an earlier phase, before damages such as erosions occur. It can

be estimated that patients having similar tender and swollen joint counts and seropositivity would probably have similar risks for having an erosive disease but the ability of the 2010 ACR/EULAR criteria to detect earlier disease, as depicted by the disease duration, also allowed the recognition of the disease before the erosions occur.

All the evidence on different treatment approaches and new molecules in RA in the last decade indicates that earlier treatment results in better patient outcomes, particularly with less damage. The extent of joint damage, especially bone erosions, have been demonstrated to be linked to the loss of function, even in a cohort of patients with early disease that are under a tight-controlled treatment (13-14). Starting with the administration of anti-TNF drugs, the treatment options scaled-up allowing a state of remission with no residual disease activity and no loss of function. It is known that most of the biological therapies that are approved and currently in use were tested in cohorts of patients diagnosed according to the 1987 ACR criteria. However, it has also been demonstrated that the effects of infliximab on the number of circulating leucocyte subsets in early vs. late RA were different, suggesting that pathogenic mechanisms change as the disease progresses (15). Therefore, the earlier identification of patients with the 2010 ACR/EULAR criteria may help us not only to treat patients at an earlier phase while a different pathogenic mechanism is occurring but also to target molecules with different modes of action.

Our study has some limitations. The relatively low number of patients in the NEW-RA and undifferentiated arthritis groups may have underpowered our results. Another limitation is the lack of identification of the subgroup of patients who fulfilled the 2010 ACR-EULAR criteria but not the 1987 criteria. In our experience, this is only a small group of patients therefore was not separated in our study.

In conclusion, the similar disease activity should ensure suitability for intervention, whereas a shorter duration and less damage should improve the outcome with patient benefit.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Leeds (West) Research Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Z.A., C.C.G., J.N., J.F., S.H., R.J.W., P.E.; Design - S.Z.A., C.C.G., J.N., J.F., S.H., R.J.W., P.E.; Supervision - P.E.; Data Collection and/or Processing - S.Z.A., C.C.G., J.N., J.F., S.H., R.J.W.; Analysis and/or Interpretation - S.Z.A., C.C.G., J.N., J.F., S.H., R.J.W., P.E.; Literature Search - S.Z.A.; Writing Manuscript - S.Z.A., C.C.G., J.N., J.F., S.H., R.J.W., P.E.; Critical Review - S.Z.A., C.C.G., J.N., J.F., S.H., R.J.W., P.E.

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