Japanese Journal of Radiology (2019) 37:793–797
https://doi.org/10.1007/s11604-019-00870-y

ORIGINAL ARTICLE

Detecting joints with erosion(s) in rheumatoid arthritis: a novel individualized-ultrasound method performs better than existing methods

York Kiat Tan[1,2,3] · HuiHua Li[4] · John Carson Allen Jr.[5] · Julian Thumboo[1,2,3]

Received: 9 July 2019 / Accepted: 1 September 2019 / Published online: 14 September 2019

Abstract

Purpose To determine if a novel individualized-ultrasound (IUS) method can detect more joints with erosion(s) in rheumatoid arthritis (RA) patients versus existing methods.

Materials and methods The IUS method selects up to 7 or 14 ultrasonographically most inflamed joints whereas existing methods pre-fix 7 or 14 joints for ultrasonography. Using ultrasonography, the mean total inflammatory score (TIS), mean number of affected joints and mean number of joints with erosion(s) were compared between novel and existing methods among 30 RA patients using the paired Student *t* test.

Results Using 7-joint approach, comparing IUS versus existing methods, the mean (95% CI) for TIS, number of affected joints, and number of joints with erosion(s) were: 2.18 (1.88, 2.48) versus 0.95 (0.78, 1.11); 7 (7, 7) versus 4.43 (3.93, 4.94); 3.20 (2.44, 3.96) versus 1.33 (0.94, 1.72), respectively. Using 14-joint approach, comparing IUS versus existing methods, the mean (95% CI) for TIS, number of affected joints, and number of joints with erosion(s) were: 3.17 (2.75, 3.6) versus 1.71 (1.38, 2.04); 13.5 (13.05, 13.95) versus 8.13 (7.24, 9.02); 4.23 (3.13, 5.34) versus 2.77 (2.03, 3.50), respectively. *p* values all < 0.0001.

Conclusions A novel IUS method detects substantially more joints with erosion(s) in RA patients versus existing methods.

Keywords Rheumatoid arthritis · Bone erosions · Ultrasonography · Synovitis · Joints

Introduction

In rheumatoid arthritis (RA), it is known that joint inflammation drives bone destruction. Therefore, early and effective suppression of joint inflammation is an essential component of RA management [1] which would be expected to result in lesser destructive changes at the joints and leading to better patient outcome. Musculoskeletal ultrasound can be utilized as an outcome measurement tool in patients with RA [2]. Its superiority lies in its ability to directly visualize the joint pathologies of RA, including the inflamed synovium as well as structural joint damage such as bone erosions. In fact, the European League Against Rheumatism (EULAR) recommendations on the use of joint imaging in RA clinical management [3] specifically mentions that ultrasound and/or magnetic resonance imaging (MRI) should be considered if conventional radiography do not reveal damage and these may be utilized at an earlier time point to detect damage (particularly in early disease). The use of consensus ultrasound definitions of joint pathologies [4] and standardized scoring methods [5] has greatly fostered its development in RA. However, at the patient level, there is absence of general consensus on which subset(s) of joints must be included for ultrasound monitoring [6]. Using a reduced number of joints for ultrasound monitoring is less time consuming and increases the feasibility for use. Moreover, ultrasound

✉ York Kiat Tan
tan.york.kiat@singhealth.com.sg

1 Department of Rheumatology and Immunology, Singapore General Hospital, Outram Road, Singapore, Singapore

2 Duke-NUS Medical School, 8 College Rd, Singapore, Singapore

3 Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Dr, Singapore, Singapore

4 Health Services Research, Singapore General Hospital, Outram Road, Singapore, Singapore

5 Centre for Quantitative Medicine, Duke-NUS Medical School, 8 College Rd, Singapore, Singapore

monitoring of RA patients with fewer joints has also been shown to correlate well with more extended ultrasound joint monitoring [7]. In this context, a recent novel individualized-ultrasound (IUS) method, which uses ultrasonography to select the most inflamed joints for assessment, has been shown to be a highly responsive measure of joint inflammation in RA when compared to methods currently in existence that utilize pre-determined joint sites for ultrasonography [8, 9]. However, the novel IUS method has not been evaluated for structural joint damage assessment. Therefore, we aim to evaluate this in our present study. We hypothesize that a novel IUS method, by choosing the most inflamed joints on ultrasonography for evaluation, will be able to detect more joints with erosion(s) in patients with RA when compared to methods currently in existence that utilize pre-determined joint sites for ultrasonography.

Materials and methods

RA patients with at least one swollen and/or tender joint were recruited from March 2016 to January 2017 in this study which has been approved by our local institutional review board (IRB). Informed consent was obtained from all subjects prior to enrolment into the study.

Patients' clinical data

The following patient baseline clinical information were retrieved from medical records obtained from the hospital: age, gender, ethnicity, corticosteroid and disease-modifying anti-rheumatic drug (DMARD) use, disease activity score at 28 joints (DAS28) and disease duration prior to enrolment.

Ultrasound joint assessment

Ultrasound scanning in line with the EULAR guidelines [10] were carried out using the Philips Medical Systems EPIQ 5G machine (with a 5–18 MHz multi-frequency linear probe) at the same outpatient research site. The ultrasound machine was pre-set at the various joint locations used in the study with the following Doppler settings: pulse repetition frequency settings of 700–850 Hz; Doppler frequency settings of 8–9.3 MHz. Table 1 shows the joint locations scanned in this study. Ultrasound image acquisition and scoring were carried out by one rheumatologist trained in musculoskeletal ultrasonography. At the joint recesses, ultrasound power Doppler (PD) and grey-scale (GS) joint inflammatory findings were semi-quantitatively scored (none = 0, mild = 1, moderate = 2 and severe = 3). PD scoring was based on definitions by Backhaus et al. [11]. GS scoring was based on an ultrasonographic atlas [12]. As the volar recesses of the finger joints were not included in the atlas, therefore, GS scoring of these joint recesses was based on definitions by Backhaus et al. [11]. Ultrasound-detected joint erosion(s) was scored as either yes = 1 or no = 0) at the joint recesses according to the EULAR outcome measure in rheumatology (OMERACT) consensus definition of bone erosion by Wakefield et al. [4].

Novel IUS and existing ultrasound methods

Adopting the 7- or 14-joint approaches, an IUS method chooses up to 7 or 14 most inflamed joints on ultrasonography from the 36 candidate joints listed in Table 1. At each individual joint, the inflammatory joint score (IJS) is calculated by adding all the GS and PD joint inflammation

Table 1 Joint sites used in novel IUS and existing methods

Joints scanned, bilateral	Site/recesses	7-Joint approach		14-Joint approach	
		Novel IUS	Existing (clinically dominant side)	Novel IUS	Existing (bilateral sides)
Elbow	Humeroradial and Posterior fossa	Selects up to 7 most affected joints	–	Selects up to 14 most affected joints	–
Wrist	Radiocarpal (dorsal), intercarpal (dorsal) and distal radioulnar (dorsal)		Yes		Yes
MCPJ 1–5	Dorsal and volar		Yes. MCPJ 2 and 3 only		Yes. MCPJ 2 and 3 only
Thumb IPJ	Dorsal and volar		–		–
PIPJ 2–5	Dorsal and volar		Yes. PIPJ 2 and 3 only		Yes. PIPJ 2 and 3 only
Ankle	Anterior tibiotalar		–		–
MTPJ 1–5	Dorsal		Yes MTPJ 2 and 5 only		Yes MTPJ 2 and 5 only

IUS individualized-ultrasound, *MCPJ* metacarpophalangeal joint, *IPJ* interphalangeal joint, *PIPJ* proximal interphalangeal joint, *MTPJ* metatarsophalangeal joint

component sub-scores at the specific joint recess(es) divided by the greatest possible PD and GS joint inflammation score for each individual joint. This equalizes score weights across the joints [8]. Thereafter, joint selection (see Fig. 1) follows a sequence that initially ranks IJSs from the candidate joints in progressively smaller order of magnitude [8]. Joints showing the highest IJS are chosen first, with joint selection following a pre-determined order, i.e., selecting from the right and then the left beginning from smaller to larger joints in the following sequence: 1st to 5th metacarpophalangeal joints, 1st interphalangeal joint and 2nd to 5th proximal interphalangeal joints, 1st to 5th metatarsophalangeal joints, wrist, ankle and elbow. This process continues repeatedly for smaller and smaller IJSs until the attainment of the desired number of joints (e.g., until attaining 7 or 14 joints). In contrast, the methods currently in existence utilize a pre-determined 7-joint count set [11] and a 14-joint count set [6] for ultrasonography assessment (see Table 1 for the joint sites/recesses scanned).

Statistical analysis

For both the 7- and 14-joint approaches, given the specific joints included in the novel and existing methods, the IJSs were summed up per patient to derive a total inflammatory score (TIS) for each method [8]. The mean TIS, mean number of affected joints (i.e., joints with IJS > 0), and mean number of joints with erosion(s) were compared between novel and existing methods using the paired Student *t* test. Statistical analyses were performed using R 3.4.2 (https://cran.r-project.org).

Results

Patient's baseline characteristics

The mean age of the 30 RA patients was 61.7 years. Most of the patients were female (93.3%) and most of the patient were Chinese in ethnicity (76.7%). At baseline, the mean DAS28 was 3.58 (with a standard deviation of 1.20) while the patients' mean disease duration was 70.3 months (with a standard deviation of 61.2 months); 27 patients (90%) were on one or more DMARD(s) (which included methotrexate, leflunomide, sulfasalazine and hydroxychloroquine), while 22 patients (73.3%) were on prednisolone.

Novel IUS versus existing methods

Adopting the 7-joint approach, results for the mean (95% CI) TIS for the novel IUS method and the method currently in existence were 2.18 (1.88, 2.48) versus 0.95 (0.78, 1.11), respectively, with the mean difference (95% CI) 1.23 (1.04, 1.43) ($p < 0.0001$). Mean (95% CI) numbers of affected joints for the novel IUS method and the method currently in existence were 7 (7, 7) and 4.43 (3.93, 4.94), respectively, with the mean difference (95% CI) 2.57 (2.06, 3.07) ($p < 0.0001$). The mean (95% CI) number of joints with erosion(s) for the novel IUS method and the method currently in existence were 3.20 (2.44, 3.96) and 1.33 (0.94, 1.72), respectively, with mean difference (95% CI) 1.87 (1.35, 2.38) ($p < 0.0001$) (Table 2).

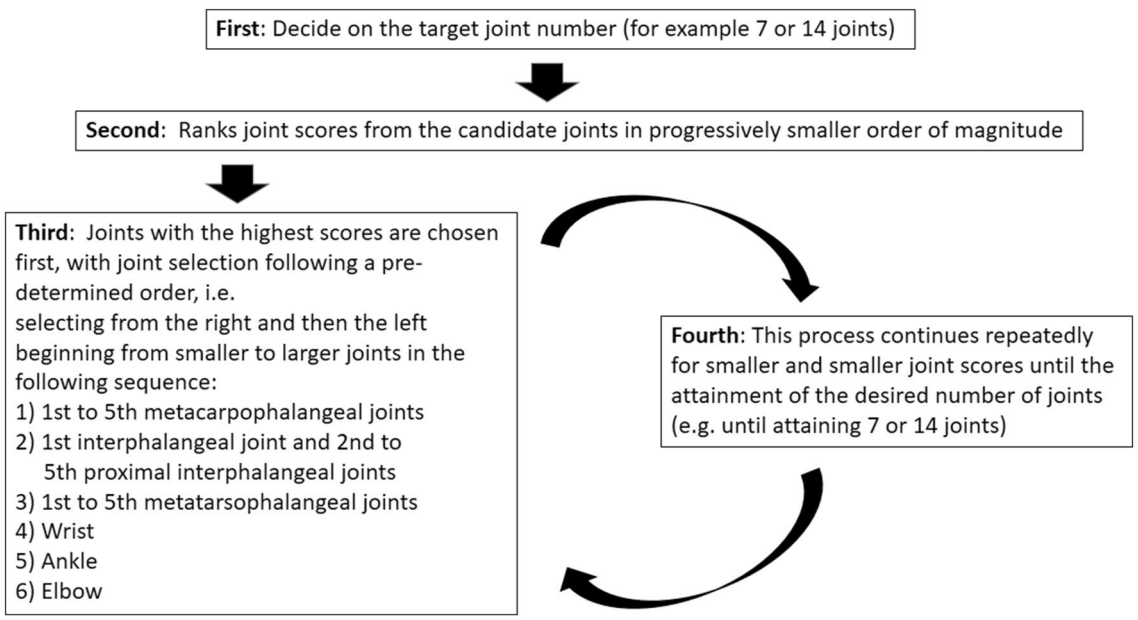

Fig. 1 Steps involved in the joint selection for individualized-ultrasound method

Table 2 Comparison of novel IUS and existing methods

Ultrasound joint approach	Mean (95% CI)			*p* value
	Novel IUS method	Existing method	Difference between novel IUS method and existing method	
Total inflammatory score				
7-Joint approach	2.18 (1.88, 2.48)	0.95 (0.78, 1.11)	1.23 (1.04, 1.43)	< 0.0001***
14-Joint approach	3.17 (2.75, 3.6)	1.71 (1.38, 2.04)	1.47 (1.30, 1.64)	< 0.0001***
Number of affected joints				
7-Joint approach	7 (7, 7)	4.43 (3.93, 4.94)	2.57 (2.06, 3.07)	< 0.0001***
14-Joint approach	13.5 (13.05, 13.95)	8.13 (7.24, 9.02)	5.37 (4.67, 6.06)	< 0.0001***
Number of joints with erosion(s)				
7-Joint approach	3.20 (2.44, 3.96)	1.33 (0.94, 1.72)	1.87 (1.35, 2.38)	< 0.0001***
14-Joint approach	4.23 (3.13, 5.34)	2.77 (2.03, 3.50)	1.47 (0.97, 1.96)	< 0.0001***

IUS individualized-ultrasound

***Statistically significantly greater for novel IUS versus existing methods

Adopting the 14-joint approach, results for the mean (95% CI) TIS for the novel IUS method and the method currently in existence was 3.17 (2.75, 3.6) versus 1.71 (1.38, 2.04), respectively, with the mean difference (95% CI) 1.47 (1.30, 1.64) ($p < 0.0001$). The mean (95% CI) numbers of affected joints for the novel IUS method and the method currently in existence were 13.5 (13.05, 13.95) and 8.13 (7.24, 9.02), respectively, with the mean difference (95% CI) 5.37 (4.67, 6.06) ($p < 0.0001$). The mean (95% CI) numbers of joints with erosion(s) for the novel IUS method and the method currently in existence were 4.23 (3.13, 5.34) versus 2.77 (2.03, 3.50), respectively, with the mean difference (95% CI) 1.47 (0.97, 1.96) ($p < 0.0001$) (Table 2).

Discussions

Our study is the first to report that a novel IUS joint selection method can detect substantially more joints with erosion(s) in patients with RA as compared to methods currently in existence that use pre-determined joint sets for ultrasonography. As joint inflammation drives the formation of bone erosions [13, 14], it is unsurprising that the novel IUS method, by detecting a greater number of ultrasonographically inflamed joints, has performed better than the existing methods in detecting joints with erosion(s).

The utilization of ultrasound to detect joint erosions in RA has been studied in relation to other imaging modalities [15] like conventional radiography (CR), computed tomography (CT) as well as magnetic resonance imaging (MRI) demonstrating evidence of construct validity. In the study by Døhn et al. [16], ultrasound was compared to CT, the gold standard imaging modality for detecting joint erosion in RA. Unilateral 2nd to 5th MCPJs in 4 healthy controls and 17 subjects with RA were imaged and evaluated for the presence of bone erosions. When compared to CT, ultrasound was shown to have moderate sensitivity (42%) but high specificity (91%) for detecting MCPJ erosions in RA. In a separate study by Wakefield et al. [17], the use of ultrasound was compared to the use of CR in detecting joint erosions in the MCPJs of 100 RA subjects. Ultrasound detected significantly more erosions (i.e., 127 erosions in 56 subjects) than CR, which detected 32 erosions in 17 subjects. Among subjects with early disease, 6.5-fold more joint erosions were detected through the use of ultrasonography when compared to CR, in 7.5-fold the number of subjects. Among subjects with longer disease duration, the corresponding differences were reported to be 3.4-fold and 2.7-fold, respectively. Ultrasound-detected erosions not seen on CR were shown to correspond by site to MRI abnormalities. Additionally, in this study by Wakefield et al. [17], ultrasonography was shown to have good intra-rater and inter-rater reliability with reported Cohen-kappa values of 0.75 and 0.76, respectively.

Our study has its limitations. We have presented data at only one time-point. Therefore, future longitudinal studies comparing novel and pre-fixed approaches in monitoring joint erosions at multiple time-points will be required. Our novel IUS method requires an ultrasonography of 36 joints at baseline (which requires more time) to help select the target joints. It is expected that subsequent follow-up re-scanning of the selected target joints will be less time consuming in comparison to the baseline ultrasound scan given that fewer joints will be involved in the re-scanning. The time saved, in this context, will also need to be assessed by future RA studies with ultrasonography performed at more than one-time point. The patients in our study cohort, on average, had longstanding disease and moderate disease activity (on DAS28). Moreover, only conventional DMARDs were included. Hence, it will be necessary to test/validate the use of the novel IUS method in other clinical settings, patient's

treatment and disease profiles in future studies. Despite our small sample size, the novel IUS method has detected a greater number of joints with erosion(s) when compared to the methods currently in existence and the results were highly statistically significant. This implies robustness of our results and suggest that they are not likely to be derived from chance. Although the issue of reproducibility assessment of the IUS method, including for ultrasound bone erosion detection, is not specifically addressed in our current small scale study, such reproducibility testing will need to be further performed on separate larger RA cohort(s). Another limitation of our study is the use of ultrasonography as the only imaging modality to assess bone erosion. Future RA studies should also include other modalities such as X-ray, CT and/or MRI for further validation and comparative analysis.

In conclusion**,** the findings from our study suggest that a novel IUS method has performed substantially better than existing methods in detecting joints with bone erosion(s) among RA patients. If the novel IUS method is proven to be useful in larger longitudinal study cohorts, it can potentially influence the selection of ultrasound models using a reduced joint count for RA ultrasound joint damage assessment.

Acknowledgements The authors would like to thank the colleagues and the staff from the study site for all the support and help that has been rendered in the conduct of this research study.

Funding Nil.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960–77.
2. Baker JF, Tan YK, Conaghan PG. Monitoring in established RA: role of imaging and soluble biomarkers. Best Pract Res Clin Rheumatol. 2015;29(4–5):566–79.
3. Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):804–14.
4. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485–7.
5. Tan YK, Conaghan PG. Imaging in rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2011;25:569–84.
6. Mandl P, Naredo E, Wakefield RJ, Conaghan PG, D'Agostino MA, OMERACT Ultrasound Task Force. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. J Rheumatol. 2011;38:2055–62.
7. Naredo E, Gamero F, Bonilla G, Uson J, Carmona L, Laffon A. Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: comparison of extended versus reduced joint evaluation. Clin Exp Rheumatol. 2005;23:881–4.
8. Tan YK, Allen JC Jr, Lye WK, Conaghan PG, D'Agostino MA, Chew LC, et al. Novel ultrasound joint selection methods using a reduced joint number demonstrate inflammatory improvement when compared to existing methods and disease activity score at 28 joints. J Rheumatol. 2016;43:34–7.
9. Tan YK, Allen JC Jr, Lye WK, Conaghan PG, Chew LC, Thumboo J. Dichotomous versus semi-quantitative scoring of ultrasound joint inflammation in rheumatoid arthritis using novel individualized joint selection methods. Clin Rheumatol. 2017;36:1137–41.
10. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60:641–9.
11. Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009;61:1194–201.
12. Hammer HB, Bolton-King P, Bakkeheim V, Berg TH, Sundt E, Kongtorp AK, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:1995–8.
13. Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum. 2003;48:64–71.
14. Østergaard M, Hansen M, Stoltenberg M, Gideon P, Klarlund M, Jensen KE, et al. Magnetic resonance imaging determined synovial membrane volume as a marker of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis. Arthritis Rheum. 1999;42:918–29.
15. Szkudlarek M, Terslev L, Wakefield RJ, Backhaus M, Balint PV, Bruyn GA, et al. Summary findings of a systematic literature review of the ultrasound assessment of bone erosions in rheumatoid arthritis. J Rheumatol. 2016;43:12–211.
16. Døhn UM, Ejbjerg BJ, Court-Payen M, Hasselquist M, Narvestad E, Szkudlarek M, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. Arthritis Res Ther. 2006;8:R110.
17. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000;43:2762–70.