

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

York Kiat Tan, John C. Allen Jr., Weng Kit Lye, Philip G. Conaghan, Maria Antonietta D'Agostino, Li-Ching Chew, and Julian Thumboo

ABSTRACT. *Objective.* A pilot study testing novel ultrasound (US) joint-selection methods in rheumatoid arthritis. *Methods.* Responsiveness of novel [individualized US (IUS) and individualized composite US (ICUS)] methods were compared with existing US methods and the Disease Activity Score at 28 joints (DAS28) for 12 patients followed for 3 months. IUS selected up to 7 and 12 most ultrasonographically inflamed joints, while ICUS additionally incorporated clinically symptomatic joints. *Results.* The existing, IUS, and ICUS methods' standardized response means were -0.39 , -1.08 , and -1.11 , respectively, for 7 joints; -0.49 , -1.00 , and -1.16 , respectively, for 12 joints; and -0.94 for DAS28. *Conclusion.* Novel methods effectively demonstrate inflammatory improvement when compared with existing methods and DAS28. (First Release December 1 2015; J Rheumatol 2016;43:34-7; doi:10.3899/jrheum.150590)

Key Indexing Term:

RHEUMATOID ARTHRITIS

ULTRASOUND

SYNOVITIS

Ultrasonography (US) is increasingly used to monitor joint inflammation in rheumatoid arthritis (RA)¹. The optimal method of selecting reduced joint counts for US monitoring is not established. Various criteria have been used for reduced joint selection (e.g., frequency of involvement, feasibility, representativeness of joints, logistic regression models)². Scanning fewer joints saves time³ and yet can be representative of the inflammatory changes using extended scanning⁴. A systematic review studying US joint counts in RA² highlighted 2 existing methods^{5,6} with good validity: 1 using a predefined 7-joint count⁵ and another using a 12-joint count derived out of using US reduction from the frequency of

inflammatory involvement from 44 joints⁶. Because the extent and distribution of affected joints differ between individuals, such methods do not ensure selection of the most affected joints or the greatest number of affected joints per individual for US monitoring.

In our pilot study, novel individualized joint selection methods are designed to improve the number of affected joints per patient for US scanning (limited by a target joint number). The novel individualized US (IUS) method selects up to 7 and 12 most inflamed joints detected on US, while the novel individualized composite US (ICUS) method additionally incorporates clinically symptomatic joints. The

From the Department of Rheumatology and Immunology, Singapore General Hospital; Office of Clinical Sciences, Centre for Quantitative Medicine, Duke-National University of Singapore (NUS) Graduate Medical School, Singapore; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK; Department of Rheumatology, Assistance Publique – Hôpitaux de Paris (APHP), Hôpital Ambroise Paré, Boulogne-Billancourt; Institut national de la santé et de la recherche médicale (INSERM) U1173, Laboratoire d'Excellence INFLAMEX, Université de Versailles St.-Quentin-en-Yvelines, Montigny-le-Bretonneux, France.

Grant support from the Khoo Clinical Scholars Pilot Award.

Y.K. Tan, MBBS, MMED, MRCP, Consultant, Department of Rheumatology and Immunology, Singapore General Hospital, and Adjunct Assistant Professor, Duke-NUS Graduate Medical School, and Clinical Senior Lecturer, Yong Loo Lin School of Medicine, National University of Singapore; J.C. Allen Jr, PhD, Office of Clinical Sciences, Centre for Quantitative Medicine, Duke-NUS Graduate Medical School Singapore; W.K. Lye, MSc, Office of Clinical Sciences, Centre for Quantitative Medicine, Duke-NUS Graduate Medical School Singapore;

P.G. Conaghan, MBBS, PhD, FRACP, FRCP, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds Musculoskeletal Biomedical Research Unit; M.A. D'Agostino, MD, PhD, Professor of Rheumatology, APHP, Department of Rheumatology, Hôpital Ambroise Paré, and INSERM U1173, Laboratoire d'Excellence INFLAMEX, Université de Versailles St.-Quentin-en-Yvelines; L.C. Chew, BMED, SCI, MBBS, MRCP, FAMS, Senior Consultant, Department of Rheumatology and Immunology, Singapore General Hospital, and Adjunct Assistant Professor, Duke-NUS Graduate Medical School, and Clinical Senior Lecturer, Yong Loo Lin School of Medicine, National University of Singapore; J. Thumboo, MBBS, MMED, MRCP, FAMS, FRCP, Vice Chair for Research, Medicine Academic Clinical Programme, and Senior Consultant, Department of Rheumatology and Immunology, Singapore General Hospital, and Professor, Duke-NUS Graduate Medical School, and Adjunct Professor, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

Address correspondence to Dr. Y.K. Tan, Department of Rheumatology and Immunology, Singapore General Hospital, Outram Road, Singapore 169608. E-mail: tan.york.kiat@singhealth.com.sg

Accepted for publication September 30, 2015.

key feature is joint selection dictated by severity, beginning with the most severely affected joint and continuing until the target count is reached. Target joint limits were set at 7 and 12 to maintain consistency with joint counts specified by existing methods^{5,6}. We hypothesized that the novel methods would improve experimental efficacy, resulting in greater sensitivity for detecting change when compared with existing methods and the Disease Activity Score at 28 joints (DAS28).

MATERIALS AND METHODS

Patients. Seropositive patients with RA (DAS28 > 3.2) with ≥ 5 tender and/or swollen joints starting or escalating disease-modifying antirheumatic drugs (DMARD) and corticosteroid therapy in the rheumatology unit at the Singapore General Hospital were enrolled from March 2013 to May 2014 and followed up for 3 months. The local institutional review board approved this pilot study. Patients gave written informed consent. Patients were excluded if they had connective tissue diseases, other inflammatory arthritides, pregnancy, Hepatitis B/C, previous joint replacements, or a limb amputation.

At 0 and 3 months, a 44-joint clinical assessment (by a metrologist) and US were performed on the same day. A rheumatologist experienced in musculoskeletal US (blinded to the metrologist's findings) acquired and scored the US images.

Clinical assessment. Joints assessed for tenderness and pain included bilateral shoulders, elbows, wrists, metacarpophalangeal joints (MCPJ) 1–5, proximal interphalangeal joints 2–5, thumb interphalangeal joint, hips, knees, ankles, midtarsal, and metatarsophalangeal joints 1–5. Of these 44 joints, 40 were assessed for swelling (hips and midtarsals excluded using the approach of DAS44⁷). Joint tenderness and swelling were scored as 1 = yes and 0 = no. Joint pain was scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. These scores form the clinical subscores used in the ICUS method (further described under the section “Individualized methods”).

US evaluation. US was performed with General Electric Healthcare LOGIQe machine with a multifrequency linear array transducer (5–13

MHz) or Philips Medical Systems EPIQ 5G machine with a multifrequency linear array transducer (5–17 MHz). US outpatient facility, machine, probe, and settings were kept the same for each patient. Standardized scanning was based on the European League Against Rheumatism (EULAR) guidelines⁸. The joint/tendon sites scanned are listed in Table 1. US pathology definitions from the EULAR OMERACT (Outcome Measures in Rheumatology) US workgroup were used¹. Greyscale synovial hypertrophy (SH) and power Doppler (PD) vascularity were scored semiquantitatively (0 = none, 1 = mild, 2 = moderate, 3 = severe) based on US scoring definitions used by Backhaus, *et al*⁵. This method was used at the hand and feet joints (because these joints were included in the study by Backhaus, *et al*) and extrapolated for use in other joints (including the elbow, knee, ankle, midtarsal, shoulder, and hip). However, at certain medium-sized joints (e.g., elbow, knee, and ankle) whereby relevant images from a scoring atlas⁹ are available, semiquantitative scoring (0 to 3) was performed based on the relevant images from the scoring atlas. The shoulder and hip joints were not included in the original study by Backhaus, *et al* or the atlas, so where applicable, a score of 0 (normal) was taken to be greyscale SH less than the mean plus 2 SD of normal range¹⁰. Tenosynovitis was scored as 1 = yes and 0 = no for greyscale and PD findings. These scores form the US subscores used in the existing and individualized methods (further described under the sections “Existing methods” and “Individualized methods”).

Existing methods. The existing methods include the 7 and 12 joints used by Backhaus, *et al*⁵ and Naredo, *et al*⁶, respectively (Table 1). The individual joint score (IJS) per joint was calculated as the sum of the US subscores divided by the maximum possible score at that joint, so as to equalize score weights across the joints. The maximum number of affected joints selected by the existing 7- and 12-joint methods are therefore 7 and 12, respectively.

Individualized methods. In the 7-joint approach, the individualized methods selected up to a maximum of 7 most affected joints for monitoring. In the 12-joint approach, the individualized methods selected up to a maximum of 12 most affected joints for monitoring. For the IUS method, the IJS at each joint was calculated as the sum of the US subscores divided by the maximum possible score at that joint. For the ICUS method, the IJS at each joint was calculated as the sum of the clinical and US

Table 1. Joint and tendon sites used in the individualized and existing methods.

Joints/tendons Scanned, Bilateral	Sites/Recesses	7-joint Approach		12-joint Approach	
		Individualized	Existing (clinically dominant side)	Individualized	Existing (bilateral)
1. Shoulder	Axillary/posterior		—		—
2. Elbow	Humeroradial, humeroulnar, posterior fossa		—		Yes
3. Wrist, and ED/ECU/FD tendons	Radiocarpal (dorsal/volar), intercarpal/ulnocarpal (dorsal)		Yes		Yes
4. MCPJ 1–5, and flexor tendons	Dorsal/volar	Selects up to 7 most affected joints for monitoring	Yes, MCPJ 2 and 3	Selects up to 12 most affected joints for monitoring	Yes, MCPJ 2 and 3
5. PIPJ 2–5	Dorsal/volar		Yes, PIPJ 2 and 3		—
6. Thumb IPJ	Dorsal/volar		—		—
7. Hip	Anterior		—		—
8. Knee	Suprapatellar, lateral/medial recess		—		Yes
9. Ankle, and lateral/medial tendons	Anterior tibiotalar		—		Yes
10. Midtarsal	Talonavicular, cuneonavicular		—		—
11. MTPJ 1–5	Dorsal		Yes, MTPJ 2 and 5		—

ED: extensor digitorum; ECU: extensor carpi ulnaris; FD: flexor digitorum; MCPJ: metacarpophalangeal joints; PIPJ: proximal interphalangeal joints; IPJ: interphalangeal joints; MTPJ: metatarsophalangeal joints.

subscores divided by the maximum possible score at that joint. An affected joint for the existing and individualized methods was defined as IJS > 0.

The joint selection process (Figure 1) was as follows: the IJS from the 44 joints were ranked from largest to smallest score. The target joint count was set at 7 and 12. Joints with the highest IJS were identified. Joint selection progressed from the small to medium and larger joints as described in Figure 1. This process was repeated using joints with decreasing IJS until the target joint count was reached. The rationale for this joint selection process was (1) RA frequently involves the small joints, (2) scanning small joints is often easier, and (3) the semiquantitative scoring method was developed using smaller joints¹¹.

Statistical analysis. For the above methods, the IJS from the selected joints were summed to obtain a total inflammatory score (TIS) per patient. Patients' mean TIS were calculated at 0 and 3 months and were used for deriving the standardized response mean (SRM), calculated as the mean change in the TIS score divided by the SD of the change in the TIS score. The threshold values from Cohen for effect size (ES) are often used for interpretation, i.e., trivial [ES < 0.20, small (0.20 ≤ ES < 0.50), moderate (0.50 ≤ ES < 0.80), and large (ES ≥ 0.80)]^{12,13,14,15}. The average number of affected joints at baseline by these methods was reported. The SRM (at 3 mos) were calculated for these methods and the DAS28.

RESULTS

Patient characteristics. Twelve patients with RA [mean (SD) age 57.6 (6.5) yrs, 83.3% women, 83.3% Chinese, 8.3% Indian, and 8.3% other ethnic groups] with mean (SD) disease duration at baseline of 55.8 (71.2) months completed the study. All patients were started or escalated with DMARD and corticosteroid therapy prior to the baseline US scans. Within 3 months prior to recruitment, 8 patients (66.7%) were receiving oral DMARD (which included methotrexate, sulfasalazine, hydroxychloroquine, and azathioprine) while 11 patients (91.7%) were receiving prednisolone. The mean

DAS28 at baseline and 3 months was 5.21 and 4.32, respectively. The SRM for DAS28 was -0.94.

Seven-joint and 12-joint approaches. Using 7 joints, the affected joints (average number) for the existing, IUS, and ICUS methods were 3, 7, and 7, respectively, with corresponding SRM of -0.39, -1.08, and -1.11.

Using 12 joints, the affected joints (average number) for the existing, IUS, and ICUS methods were 7, 11, and 12, respectively. The SRM were -0.49, -1.00, and -1.16, respectively (Table 2).

DISCUSSION

Our novel methods using a reduced joint number effectively demonstrate inflammatory improvement when compared with existing methods and the DAS28. This is unsurprising, given our emphasis on selecting affected joints (i.e., selecting as many affected joints, beginning with the most severely affected ones, until the target joint limit is reached) for followup scanning.

The SRM of the existing methods was consistent with the SRM reported in 2 RA studies^{12,13} using US monitoring. The SRM was -0.2595 at 5 months in 1 study¹² using US of bilateral MCPJ 1-5 and -0.46 at 3 months in another study¹³ using US at the dominant wrist.

Our individualized methods required a 44-joint US assessment at baseline to select the target joints. While this means additional time at the baseline scan, followup scans require less time when compared with the baseline scan because only the selected joints need rescanning.

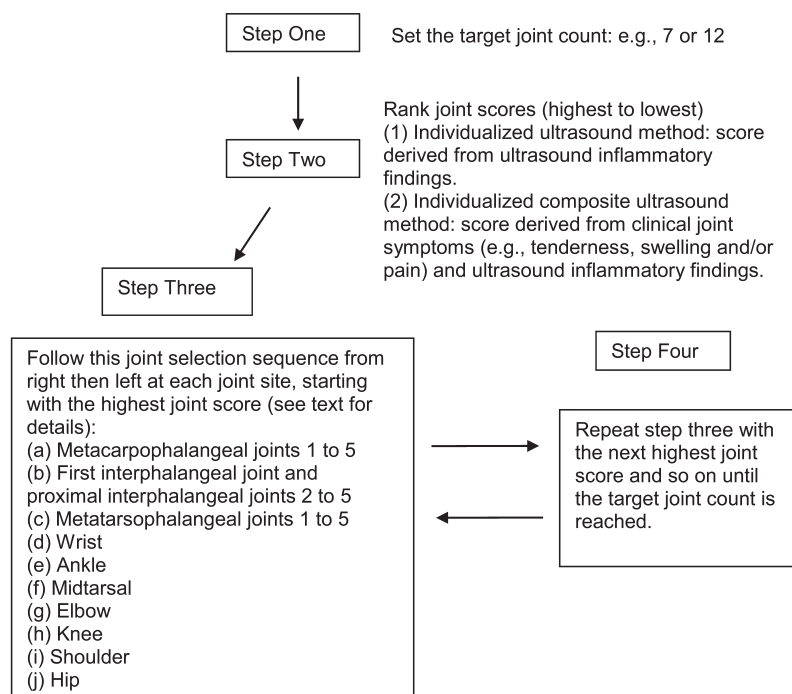


Figure 1. Individualized methods of the joint selection process.

Table 2. Results of the individualized and existing methods.

No. Joints	Scoring Method							
	IUS		ICUS		Existing		DAS28	
	Baseline	Third Mo	Baseline	Third Mo	Baseline	Third Mo	Baseline	Third Mo
7-joint[#]								
Average no. affected joints*	7		7		3			
Mean (SD) [^]	2.14 (1.17)	1.42 (0.76)	2.06 (0.90)	1.21 (0.68)	0.47 (0.32)	0.38 (0.25)	5.21 (0.66)	4.32 (1.00)
Median TIS (IQR)	2.00 (1.45)	1.42 (0.90)	2.07 (1.24)	1.16 (1.31)	0.42 (0.38)	0.37 (0.50)		
SRM (95% CI)		-1.08 (-1.79 to -0.34)		-1.11 (-1.83 to -0.37)		-0.39 (-0.97 to 0.21)		-0.94 (-1.68 to -0.17)
12-joint[#]								
Average no. affected joints*	11		12		7			
Mean (SD) [^]	2.70 (1.61)	1.76 (0.95)	2.81 (1.20)	1.84 (0.82)	1.46 (0.80)	1.27 (0.72)		
Median TIS (IQR)	2.48 (1.99)	1.60 (1.20)	2.74 (1.58)	1.75 (1.25)	1.55 (1.65)	1.42 (1.37)		
SRM (95% CI)		-1.00 (-1.69 to -0.29)		-1.16 (-1.89 to -0.40)		-0.49 (-1.09 to 0.12)		

[#] Refers to no. joints used in the IUS, ICUS, and existing methods (and not DAS28). * An affected joint is defined as individual joint score greater than 0. [^] For the IUS, ICUS, and existing methods, refers to mean TIS score; for DAS28, refers to the mean DAS28 score. IUS: individualized ultrasound; ICUS: individualized composite ultrasound; TIS: total inflammatory score; SRM: standardized response means; IQR: interquartile range; DAS28: Disease Activity Score at 28 joints.

Our pilot results will need to be confirmed in larger cohorts. Future studies incorporating control group(s) for comparison, as well as correlation with other patient outcomes (e.g., disease remission, structural alteration, functional prognosis) would be necessary. The number of reduced joints to assess during followup could also be explored in larger studies.

ACKNOWLEDGMENT

We thank our colleagues from the Singapore General Hospital (SGH), Department of Rheumatology and Immunology, who referred patients for our study and also the staff of the Autoimmunity and Rheumatology Centre of the SGH where this study was performed. We would also like to acknowledge funding support from the Estate of Tan Sri Khoo Teck Puat (Khoo Clinical Scholars Pilot Award).

REFERENCES

- Tan YK, Conaghan PG. Imaging in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2011;25:569-84.
- 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.
- Hammer HB, Kvien TK. Comparisons of 7- to 78-joint ultrasonography scores: all different joint combinations show equal response to adalimumab treatment in patients with rheumatoid arthritis. *Arthritis Res Ther* 2011;13:R78.
- 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.
- Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. *Arthritis Rheum* 2009;61:1194-201.
- Naredo E, Rodríguez M, Campos C, Rodríguez-Heredia JM, Medina JA, Giner E, et al; Ultrasound Group of The Spanish Society of Rheumatology. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheum* 2008;59:515-22.
- Sokka T, Pincus T. Quantitative joint assessment in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23 Suppl 39:S58-62.
- 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.
- 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.
- Schmidt WA, Schmidt H, Schicke B, Gromnica-Ihle E. Standard reference values for musculoskeletal ultrasonography. *Ann Rheum Dis* 2004;63:988-94.
- Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Østergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. *Arthritis Rheum* 2003;48:955-62.
- Kamishima T, Tanimura K, Shimizu M, Matsuhashi M, Fukae J, Kon Y, et al. Monitoring anti-interleukin 6 receptor antibody treatment for rheumatoid arthritis by quantitative magnetic resonance imaging of the hand and power Doppler ultrasonography of the finger. *Skeletal Radiol* 2011;40:745-55.
- Haavardsholm EA, Østergaard M, Hammer HB, Bøyesen P, Boonen A, van der Heijde D, et al. Monitoring anti-TNFalpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. *Ann Rheum Dis* 2009;68:1572-9.
- Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care* 1989;27 Suppl:S178-89.
- Cohen J. *Statistical power analysis for the behavioral sciences*, 2nd ed. New Jersey: Lawrence Erlbaum; 1988.