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TITLE PAGE

Title: Utility of ultrasonography in guiding modification of disease modifying anti-rheumatic drugs and steroid therapy for inflammatory arthritis in routine clinical practice.

Authors

York Kiat Tan[1], Li-Ching Chew[1], John C Allen Jr[2], Weng Kit Lye[2], Lei Lei Htay[3], Ali Hassan[4], Philip G Conaghan[5], Julian Thumboo[1]

Address of the institution at which the work was carried out

1) Department of Rheumatology and Immunology, Singapore General Hospital, Singapore

2) Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

3) Rheumatology Department, Yangon Specialty Hospital, Yangon, Myanmar

4) Internal Medicine, Brooks Hospital - Alberta Health Services, Brooks, Canada

5) Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK

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Running title: Ultrasound and inflammatory arthritis routine care

Correspondence: York Kiat Tan, Department of Rheumatology and Immunology

Singapore General Hospital, Outram Road, Singapore 169608, +65 63214028,

tan.york.kiat@singhealth.com.sg

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ABSTRACT

Objective

To determine the utility of ultrasonography in guiding modification of disease modifying anti-rheumatic drug (DMARD) and steroid therapy for inflammatory arthritis (IA) in routine clinical practice.

Methods

In this retrospective study, we analyzed DMARD and steroid use in IA patients referred to a rheumatologist-led ultrasound clinic. Power Doppler (PD) vascularity and greyscale (GS) synovial hypertrophy joint findings were categorized as positive/negative for each patient. The erythrocyte sedimentation rate (ESR) was used as a measure of disease activity.

Results

We assessed single visit data for 46 adult IA patients: 67.4% (n=31) rheumatoid arthritis (RA), 15.2% (n=7) psoriatic arthritis, 10.9% (n=5) spondyloarthritis, and 6.5% (n=3) undifferentiated IA. The mean ESR was 28.8 mm/hr. Thirty-seven patients with both GS and PD ultrasound results were subsequently analyzed. All patients (n=10) escalated and/or initiated on DMARD and 9 of 10 patients escalated or initiated on steroid were PD and GS positive. 6 of 7 patients with dose reduction and/or cessation of DMARD and 5 of 7 patients with dose reduction or cessation of steroid were PD negative. Of 6 patients with GS positive and PD negative, 3 had dose reduction and/or cessation of DMARD, while 4 had dose reduction of steroid; none of the

6 patients had DMARD/steroid escalation.

Conclusion

By clarifying joint inflammation in an IA cohort with overall low ESR, ultrasonography of physician-selected joints can improve clinical assessment resulting in treatment modification. Positive PD findings were particularly influential, while the clinical significance of GS positivity alone requires further investigation.

Key words: Inflammatory arthritis, rheumatoid arthritis, ultrasound, synovitis

INTRODUCTION

Modern management of inflammatory arthritis (IA) aims to effectively suppress joint inflammation. However there are situations when rheumatologists are uncertain whether there is underlying joint inflammation after routine clinical assessment. In such situations, ultrasonography can be utilized for more accurate evaluation [1]. Ultrasound is well suited for this as it allows direct visualization of the inflamed synovium and has been shown to be superior when compared to clinical examination in detecting inflammation [2]. It is a non-invasive, radiation-free imaging modality which permits dynamic, multi-site and multi-planar joint scanning [3, 4]. The mean detection rate for hand/wrist synovitis on ultrasound has been reported to be more than two-fold greater when compared to clinical examination in rheumatoid arthritis (RA) [5]. Ultrasound can also detect joint inflammation frequently in RA patients despite clinically defined remission; such inflammation has been shown to have prognostic significance in predicting subsequent radiographic structural progression) [6, 7].

Although there is a growing use of musculoskeletal ultrasound among rheumatologists worldwide, there is still limited literature on the use of ultrasound for directing therapy changes in “real life” routine clinical care settings. Previous studies on ultrasound performed in the rheumatology outpatient settings show that ultrasonography has an impact on the

management of patients with musculoskeletal disease [8, 9]. This study aims to add to the literature on the clinical utility of ultrasound, specifically on how ultrasound can direct disease modifying anti-rheumatic drug (DMARD) and steroid therapy changes in the routine clinical care of patients with IA.

METHODS

Patients

As part of our inclusion criteria for this retrospective observation study, we included patients with known IA referred to a rheumatologist-led musculoskeletal ultrasound clinic at the Singapore General Hospital from March 2012 to July 2013 for ultrasonography of the joint site(s) that was requested by their physicians. A standardized ultrasound referral and reporting form was utilized by the referring physicians and the reporting doctor, respectively. The ultrasound results were returned to the physicians who would then decide on the patients' medication use. For the current study, patient ultrasound imaging data were retrieved from the ultrasound reports, while demographics and clinical data were obtained from the hospital medical records. All patient data were anonymized. This study was approved by the local institutional review board (IRB) and conforms to the relevant research ethical guidelines.

Ultrasound

All scans were performed by one of two rheumatologists experienced in musculoskeletal US. The scans were performed using either a General Electric Healthcare LOGIQe machine with a

multi-frequency linear array transducer (5–13 MHz) or a Philips Medical Systems IU22 machine with a multi-frequency linear array transducer (5-17 MHz). For each patient, power Doppler (PD) vascularity and greyscale (GS) synovial hypertrophy at the requested scanned joints were categorized as positive when at least one joint site was positive for that finding, or negative when no joint site was positive for that finding. Semi-quantitative scoring of the severity of PD vascularity and GS synovial hypertrophy are commonly utilized when reporting ultrasound results. In this study, we employed a 0-5 severity scale (none, mild, mild-moderate, moderate, moderate-severe, severe) to characterize degree of PD vascularity and GS synovial hypertrophy at the joints. In the event of multiple severity scores for a single patient—which could occur when scores were present at two or more recesses in a given joint or present at two or more different joint sites—the highest severity score was chosen. The inflammatory marker erythrocyte sedimentation rate (ESR) was used as a measure of disease activity.

DMARD and steroid use

We reviewed medical records to determine the use of oral medications (DMARD and corticosteroids) within 3 months following the date of ultrasound. We specifically looked at changes in DMARD and steroid therapy—whether these were escalated, initiated, reduced and/or ceased.

Statistical analysis

Categorical variables were summarized using frequency counts and percentages, and continuous variables using mean and standard deviation (SD). There were few patients with clinical variable outcomes ≥2 (>mild) on the ultrasound severity scale, so scores ≥2 were pooled, resulting in three ultrasound severity categories (Normal, Mild, and >Mild) for the statistical analysis. A linear contrast in the context of standard ANOVA was used to test clinical variables for a significant trend in response across ultrasound severity categories. Statistical significance set at $p < 0.05$. Statistical analysis was performed using SAS version 9.3 (SAS© Inc., Cary NC, USA).

RESULTS

Patient baseline characteristics

We assessed single visit data for 46 adult IA patients: 67.4% (n=31) rheumatoid arthritis (RA), 15.2% (n=7) psoriatic arthritis, 10.9% (n=5) spondyloarthritis, and 6.5% (n=3) undifferentiated IA; mean age (SD) 53.7(14.1) years; majority female (n=36, 78.3%); Chinese (n=33, 71.7%), Malay (n=4, 8.7%), Indian (n=7, 15.2%) and other races (n=2, 4.4%); mean ESR (SD) 28.8 (25.0) mm/hr. Figure 1 shows the frequency of the joint sites scanned by ultrasound in the study cohort. Among patients with RA, 23 (74.2%) were rheumatoid factor (RF) positive, 23 (74.2%) were anti-cyclic citrullinated peptide antibodies (anti-CCP) positive. Disease activity

score 28 (DAS28) scores were available for 12 (38.7%) RA subjects and these were used to derive the mean DAS28 (SD) which was 2.92 (0.80). All patients were on conventional synthetic DMARDs (csDMARDs), 1 (3.2%) patient was on tumor necrosis factor inhibitor (anti-TNFs), 20 (64.5%) were on prednisolone and 8 (25.8%) were on non-steroidal anti-inflammatory drugs (NSAIDs) and/or Cox-II inhibitors. Among patients with psoriatic arthritis and spondyloarthritis, 4 (33.3%) patients were HLA B27 positive. 11(91.7%) patients were on csDMARDs, 1 (8.3%) patient was on anti-TNFs, 4 (33.3%) patients were on prednisolone and 7 (58.3%) patients were on NSAIDs and/or Cox-II inhibitors. 37 patients with both GS and PD ultrasound results at the joints were included in the analysis. As part of our exclusion criteria, 9 patients lacking both GS and PD ultrasound results at the joints were excluded; among them were patients with ultrasound-guided joint injection/rotator cuff tendinopathy/tendon pathologies assessment only.

DMARD and steroid use in relation to ultrasound findings

Figure 2 shows the PD and GS findings in association with DMARD and corticosteroid use in the study cohort. Among the 37 patients analyzed, all (n=10) patients escalated and/or initiated on DMARD, and 9 of 10 patients escalated or initiated on corticosteroids were PD and GS positive. 6 of 7 patients with dose reduction and/or cessation of DMARD and 5 of 7 patients with dose reduction or cessation of steroid were PD negative. Of 6 patients with GS positive

and PD negative, 3 had DMARD dose reduction and/or cessation, and 4 had corticosteroid dose reduction; none of the 6 patients had DMARD or corticosteroid escalation.

Ultrasound severity categories

The test for a linear trend on mean ESR over normal, mild and >mild ultrasound severity categories was not statistically significant. Likewise in the RA subgroup, the linear trend test on mean RF, anti-CCP and DAS28 over ultrasound severity categories was not statistically significant (Table 1).

DISCUSSION

In this study, we aimed to determine if ultrasonography influences DMARD and steroid therapy during routine care of patients with IA. We found that ultrasonography of physician-selected joints (rather than a pre-defined set of joints) can improve clinical assessment resulting in treatment modification, by clarifying joint inflammation in an IA cohort with overall low level ESRs. Physicians relied on ultrasound results (especially PD findings) when they altered DMARD and steroid therapy. On one hand, all the DMARD escalation and/or initiation and nearly all the steroid escalation or initiation occurred when PD findings were positive. On the other hand, almost all the DMARD dose reduction and/or cessation and most of the steroid dose reduction and/or cessation occurred when PD findings were negative. PD signals reflect synovial vascularity and have been found to correlate well with joint inflammation seen on

histology [10-12]. PD positivity is often taken to represent active synovitis. PD findings can be commonly detected in RA patients in clinical remission [6] and were found to predict subsequent disease flare [13-14] and radiological progression [6]. It is conceivable that PD findings helped clarify whether “active” joint inflammation was present in our study cohort. This information helped physicians decide if changes to their patients’ DMARD and steroid therapy were required.

Rheumatologists aim to accurately characterize joint inflammation in IA patients on DMARD. Musculoskeletal ultrasound is superior to clinical examination in the assessment of joint inflammation [1, 5] and can be utilized to help clarify the presence and severity of joint inflammation when there is uncertainty on routine clinical assessment. Our study adds to the existing literature by detailing how ultrasound GS and PD joint findings can influence physicians’ DMARD and steroid prescribing patterns among patients with IA managed in the routine clinic setting. As our interest was in determining how ultrasound GS and PD findings can impact on physician prescribing practice, we chose patients with both PD and GS findings available for further analysis in relation to their DMARD and steroid use. We excluded a small group of patients with no GS or PD findings as it was not possible to reliably interpret findings for these patients.

Two previous studies have reported on the use of musculoskeletal ultrasound in routine clinic settings. In the first study, 100 out of 520 consecutive rheumatology outpatients were referred for ultrasound. DMARD were changed in 13 patients based on ultrasound joint findings, of which 10 were due to the presence of extensive subclinical synovitis [8]. In the second study, ultrasound was performed in a cohort of patients selected for ultrasound at the physician's discretion. Among patients with a definite diagnosis of rheumatologic disease, ultrasound findings influenced treatment decisions in about a quarter of these patients (45 out of 165 patients). In the RA subgroup, about half (31 out of 60 patients) had their treatment influenced by their ultrasound findings [9]. A recent randomized controlled trial involving 111 untreated patients with early undifferentiated arthritis/RA tested the use of musculoskeletal ultrasound for disease activity assessment in addition to DAS28 to guide DMARD escalation strategies. In this study, the group with the additional use of musculoskeletal ultrasound experienced higher DAS44 remission rates after 18 months although there were no other improved clinical outcomes [15].

Ultrasound can provide information on the degree of severity of joint inflammation. Our study found no evidence of a trend associating higher values of the inflammatory marker ESR (which serves as an objective measure of joint inflammation in this cohort) with severity of ultrasound inflammatory findings over normal, mild and >mild severity categories. This may be explained

by the greater sensitivity of ultrasound to detect active joint inflammation (when compared to ESR) in a patient cohort with an overall low level ESRs. In another study involving 128 RA patients in clinical remission (DAS 28 $\leq$ 2.6), when more stringent DAS28 and SDAI remission thresholds were used instead of standard remission thresholds, the percentage of patients with PD vascularity was not reduced although there was a reduction in the mean swollen and tender joint counts ($p<0.001$); this suggests that clinical criteria may not be adequately sensitive in detecting low levels of joint inflammation accurately that could otherwise be detected by ultrasound [16].

In the group with positive GS but negative PD findings, there was no instance of DMARD or steroid escalation while dose reduction and/or cessation of these medications were observed. It is important to establish the true clinical significance of GS positivity without active PD synovitis (i.e. whether the presence or quantity of GS synovial hypertrophy predicts further structural joint damage) as this will have important therapeutic implications. In a study on early RA patients with active disease, ultrasound GS inflammation at the wrist was found to be an independent predictor of one year MRI erosive progression [17]. In contrast, in a separate study on RA patients with established disease, baseline ultrasound synovial findings were not predictive of erosive progression seen on US [18]. This may reflect GS representing a mixture of inflammatory and increasing amounts of fibrous tissue in established disease. In a RA study

(with the majority (56%) of patients in DAS28 remission), while baseline GS synovial hypertrophy within individual joints was predictive of radiographic progression, only PD findings were reported to be associated with higher odds of radiographic progression in asymptomatic joints [6].

Our study has limitations. It has a relatively small sample size and is observational in nature. There is substantial missing data for DAS28 which limits its usefulness as a measure of disease activity in our study population. Nonetheless, the inflammatory marker ESR does provide a measure of joint inflammation in our patient cohort and where available the DAS28 scores were also generally low. Severity description of ultrasound PD and GS findings were recorded on a 0-5 severity scale. As ultrasonography was carried out by one of the two sonographers in each ultrasound clinic session, we did not perform any inter-rater testing. It is also possible that alteration in DMARD and steroid use may have occurred outside the 3 month study period. However, if a longer period had been used, it may have been difficult to expect a relationship between DMARD and steroid alterations to the ultrasound findings. It is also possible that only the clinicians who believe in the value of ultrasound order this investigation and hence our findings may be biased towards the clinical utility of musculoskeletal ultrasound.

In summary, ultrasonography of physician-selected joints can improve clinical assessment and therapy use by clarifying the status of joint inflammation in an IA cohort with overall low levels ESR. PD findings are especially useful while the clinical significance of GS positivity alone warrants further investigation.

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Table 1. Results of clinical variables by PD and GS US severity categories

PD severity categories, Mean (SD)				
Variables	Normal	Mild	>Mild§	P-value *
	(N=7)	(N=9)	(N=7)	
RF†	136.5 (189.6)	178.9 (327.4)	98.3 (185.9)	0.780
	(N=8)	(N=9)	(N=7)	
Anti-CCP†	72.9 (84.5)	147.5 (101.6)	60.0 (74.8)	0.749
	(N=3)	(N=4)	(N=4)	
DAS28†	3.3 (0.9)	2.6 (0.6)	2.7 (0.7)	0.253
	(N=10)	(N=11)	(N=7)	
ESR‡	29.9 (19.3)	26.5 (22.8)	39.3 (27.4)	0.973
GS severity categories, Mean (SD)				
Variables	Normal	Mild	>Mild¶	P-value
	(N=4)	(N=3)	(N=7)	
RF†	136.2 (222.1)	205.7 (273.4)	30.5 (16.3)	0.328
	(N=5)	(N=3)	(N=7)	
Anti-CCP†	109.8 (88.9)	88.0 (77.8)	64.1 (91.2)	0.395
	(N=2)	(N=0)	(N=4)	
DAS28 †	3.1 (1.1)	- (-)	2.6 (0.6)	0.498
	(N=5)	(N=5)	(N=8)	
ESR‡	40.2 (14.1)	25.8 (28.2)	22.3 (16.2)	0.130

* Linear trend

† Patients with rheumatoid arthritis ‡ Patients with inflammatory arthritis

§ PD severity score 2,3,4 and 5: n=3,3,1 and 0, respectively for RF ; n=3,3,1 and 0, respectively, for anti-CCP; n= 2,1,1 and 0, respectively for DAS28 and n=3,3,1 and 0 respectively, for ESR.

¶ GS severity score 2,3,4 and 5: n=4,2,0 and 1, respectively for RF ; n=4,2,0 and 1, respectively for anti-CCP; n= 3,0,0 and 1, respectively for DAS28 and n=4,3,0 and 1, respectively for ESR.