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Trend of the Same Synovitis Changes in Rheumatoid Arthritis on Biological Therapy: Do we Really Need a Comprehensive US Assessment of Joints?

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Abstract

Purpose: Comprehensive evaluation, including multiple recesses of all accessible peripheral joints, may be overly time-consuming in daily practice and in conducting clinical trials. This study aimed to investigate serial changes in synovitis activity at different joint level by ultrasonography (US) assessment of patients with rheumatoid arthritis (RA) on biological therapy and to determine simplified method of monitoring these patients and to search the lesser time consuming and can be used in clinical practice method.

Methods: Patients with RA who received biological therapy were enrolled. All underwent power Doppler US assessment of 24 synovial sites A total of 396 joints and 792 synovial sites underwent power Doppler US assessment for five times (at baseline and at 1, 3, 6 and 12 months after biological therapy). A general lineal model was used to compare differences among the 12 sites.

Findings: Thirty-three patients, 1980 joints, and 3960 synovial sites were evaluated. There were no significant differences in grayscale (p=0.335) and PD ultrasound (p=0.623) changes in the elbow, wrist, MCP, PIP, knee, and ankle joints.

Implications: After 12 months, there are no differences among the 12 joints surveyed. It is not recommended to conduct full work-ups on more than one joint in clinical practice. Instead, a simplified joint evaluation is all that is required to avoid unnecessary time consumption.

Keywords: Biological therapy; Monitor; Rheumatoid Arthritis; Ultrasound

Introduction

The assessment of joint inflammation is essential for diagnosing and monitoring response to therapies in patients affected by inflammatory arthropathies like rheumatoid arthritis (RA). For this, the use of musculoskeletal ultrasonography (US) with the power Doppler (PD) method has increased in the past decade. Also, US is known to detect B-mode synovitis and synovial Doppler activity in RA patients treated with either synthetic or biologic disease-modifying anti-rheumatic drugs [**1-5**]. The US-detected synovitis has a predictive value in relation to radiographic damage progression [**3**] and disease flare-up or relapse [**4**]. Assessment by US ranges from wrist and hand joints [**1**,**3**,5-8] to a comprehensive examination of 44 joints [**2**,**9**].

Nonetheless, a comprehensive evaluation of multiple recesses of all accessible peripheral joints may be overly time-consuming in clinical practice and in clinical trials. The present study aimed to investigate serial changes in synovitis activity at different joint levels using US assessment on RA patients receiving biological therapy and determine possible simplified methods of monitoring these patients and to search the lesser time consuming and can be used in clinical practice method.

Methods

Patients and methods

Patients with RA, based on the 1987 ACR criteria [**10**], who received biological therapy were prospectively recruited from the out-patient rheumatology clinic. The ethics committee of the institutional review board of the Chang Gung Memorial Hospital (CGMH) approved the study, which was conducted in accordance with the Declaration of Helsinki. This prospective cohort study enrolled patients with RA aged 20-70 years received TNF-α therapy approved by the Bureau of National Health Insurance (BNHI)'. Patients with other systemic illnesses or infections were excluded.

Clinical and laboratory assessment

Patient demographics were recorded on study entry. They were evaluated for disease activity according to the DAS28 criteria. Data on serum inflammatory markers (C-reactive protein level [CRP, reference range 0-0.5 mg/dl] and Erythrocyte sedimentation rate [ESR, reference range 10-20 mm/hour]) were obtained from laboratory tests performed on the day of the clinic visit.

Ultrasonographic assessment

On the day of the clinic visit, each patient underwent a B-mode and PD assessment by a rheumatologist experienced in musculoskeletal US

but blinded to the clinical, laboratory, and radiographic data. To reduce the possibility of bias, the patients were asked not to talk about their clinical data to the US examiner. The level of darkness in the examination room was maximized.

The US assessment included 24 synovial sites in 12 joints: elbow (anterior and posterior recesses), wrist (dorsal and carpal recesses), second and third MCP (dorsal and palmar sides), knee (supra-patellar and lateral para-patellar recesses), and ankle (anterior, medial, and lateral tibio-talar recesses). These joints and synovial sites were chosen from the simplified 12-joint score previously described by Naredo et al. [11]. The presence of synovitis was assessed by greyscale synovitis (synovial hypertrophy) and PD within each joint.

Greyscale (GS) synovitis was graded 0-3 based on the system of Szkudlarek and colleagues [**12**], re-classifying the equivocal "minimal" thickening grade as normal: grade 0, normal; grade 1, synovial thickening bulging over the line linking the tops of the peri-articular bones; grade 2, grade 1 plus extension to 1 bone diaphysis; and grade 3, grade 1 plus extension to both bone diaphyses.

Synovial hyperemia was measured by PD in each recess and the maximal score graded according to Szkudlarek et al., where 0, absence; 1, isolated signals; 2, confluent signals in less than half of the synovial area; and 3, confluent signals in more than half of the synovial area. All measurements were performed at baseline and at 1, 3, 6, and 12 months after biological therapy.

Statistical analysis

Statistical analysis was performed using SPSS, version 21.0. Quantitative variables were presented as the mean ± SD and range. A general linear model was used to compare differences between the 12 sites. Statistical significance was set at $p<0.05$.

Intra-rater reliabilities were evaluated using a two-way mixed effects model using a consistency definition in which the between-measure variance was excluded from the denominator variance. Both the single measure and average measure intra-class correlation coefficients (ICC) were calculated for total scores of both GS synovitis and PDUS. In addition, weighted κ values were calculated on a joint-by-joint level for both BM and PDUS scores. The ICC and κ values were comparable such that scores >0.60 were considered good and >0.80 were very good.

	Mean	SD
Age, mean (SD), year	54.91	14.82
Female, n (%)	24/9	
Body height, cm	159.91	6.765
Body weight, kg	56.58	9.558
Body mass index kg/m2	22.01	4.07
DAS 28	7.28	0.72
ESR mm/hr	56.12	24.767
CRP mg/dl	36.582	38.7189

Table 1: Baseline clinical and laboratory characteristics of the study patients

Results

From December 2011 to December 2014, 33 patients accepted biological therapy (20 adlimumab, 9 abatacept, and 4 actemra). Among them, 1980 joints and 3960 synovial sites were evaluated. Based on their demographic, clinical, and laboratory characteristics (Table 1), the patients had a mean age of 54.91 ± 4.82 years and majority of them were female.

Their body mass index (BMI) was 22.01 ± 0.007 and mean DAS 28 was 7.28 ± 0.72. All had severe cases of RA (Table 1). The examples of serial ultrasound changes at the elbows and knees before and after biological therapy were shown in Figure 1.

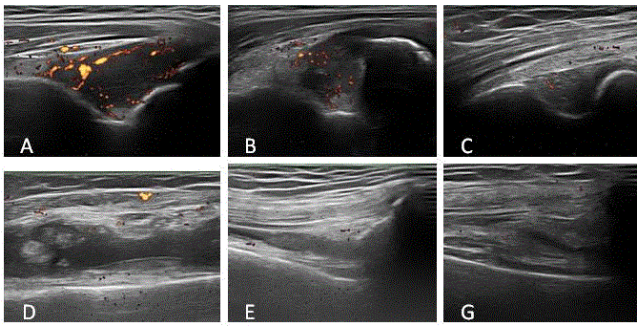

Figure 1: Longitudinal PD US of the elbow (posterior recesses), knee (supra-patellar recess) at (A,D) baseline and at (B,E) 3 and (C,F) 12 months after actemra therapy. There were signs of active synovitis with local hyper-vascularization on power Doppler modality, which improve at 3 and 12 months.

Over a 12-month period of comparison using a general linear mode to analyze the effect of the treatment on GS synovitis between all 12 joints, there were no differences in synovial hypertrophy among the bilateral elbows, wrists, second and third MCP, knees, and ankles (p=0.335) (Figure 2). Furthermore, for PD synovitis in all 12 joints, there were no differences among the elbows, wrists, second and third MCP, knees, and ankles surveyed (p=0.623) (Figure 3).

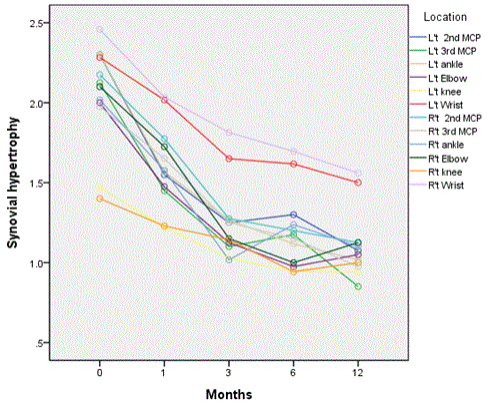

Figure 2: There were no differences in synovial hypertrophy between each joint surveyed (p=0.335).

Intra-observer reliability and sensitivity to PDUS assessment changes

For GS synovitis and PDUS, the median (range) percentages of intra-reader exact agreements were 81.6 and 65.2, respectively, and 89.9 and 79.9, respectively, of close agreements. The weighted κ values were median 0.8 for GS synovitis and 0.6 for PDUS.

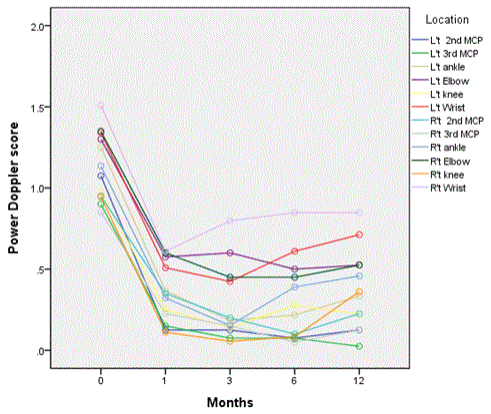

Figure 3: There were no differences in PD between each joint surveyed (p=0.623).

Discussion

Musculoskeletal US is used in diagnosing and monitoring of RA [**13-15**]. Many scoring methods have strived to reduce joint counts at B-mode and Doppler synovitis as surrogates for comprehensive US assessment for monitoring [**11**,**16-18**] or diagnosing RA [**19**].

Ultrasonographic (US) assessment has been shown to be useful in the management of RA and for monitoring the disease course [**20**]. The application of US is helpful in such evaluations and is a complementary tool for classic methods used to detect RA, such as clinical evaluation and radiography, particularly when the MCP, PIP, and MTP joints are considered [**12**,**21**,**22**].

Evidence has confirmed that GS and PD evaluation demonstrates a correlation between disease activity and degree of inflammation of synovial tissue [**23**,**24**]. Moreover, US can be used for evaluating response to biological drugs. Naredo et al. [**25**] have found a significant improvement in US parameters in RA patients undergoing therapy with a TNF blocking agent. Thus, US evaluation may be a valid method for monitoring response to biological therapy in RA patients.

However, which joints and synovial recesses are appropriate for studying and monitoring RA patients remains unknown. Hammer et al. suggested a 78-joint US assessment [**26**]. They evaluated 20 RA patients on adalimumab and found an association between US scores and clinical and laboratory parameters [**26**] The US detected more inflamed joints when compared to clinical assessment. However, the average time for each US examination was approximately 70 minutes. As such, this time-consuming process is not suitable for daily clinical practice [**26**].

Dougados et al. [**27**] conducted a US evaluation that included DAS-28 plus the MTP joints. They found that US evaluation of synovitis could represent an outcome measure that was at least as good as, and possibly more accurate than, a physical examination. The time spent by investigators in collecting US data ranged from 10 to 25 minutes [**27**].

Backhaus et al. [**16**] used a US7 score involving the wrist, the second and third MCP, the second and third PIP, and the second and fifth MTP joints of the clinically dominant side of RA patients. They found a significant correlation between changes in the US parameters for synovitis and DAS-28. This US7 score suggests a valuable tool for US examination of inflamed joint activity with reduced examination time (10-20 min) in rheumatologic diseases.

Naredo and colleagues [**11**] developed a simplified assessment evaluating 12 joints. This simplified US assessment had good content and construct validity. The mean time spent on the 12 joint US examinations was 22 minutes [**11**].

This study applied the same process of data reduction used by Naredo et al. [**11**] to investigate the validity, responsiveness, and feasibility of a one-joint US score in assessing joint inflammation. The results show that a reduced US assessment may efficiently contribute to the detection of inflammation. Therefore, it is not necessary to conduct a work-up of more than one joint in clinical practice.

We have verified additional information regarding PDUS scores in patients with RA. For better clinical availability, we have reduced the number of sites examined by US to only six sites of the wrist and finger joints. These methods are simple and can save time that would be spent on scanning. Since the correlation of disease activity and PDUS was weaker than those with 24 synovial sites, further studies with larger numbers of patients should be necessary.

The application of the US assessment in clinical practice should include a comprehensive evaluation of patient inflammatory status and feasibility in order to reduce the time needed for US examination. The importance of testing the feasibility of US is included in the research agenda of the OMERACT US task force in 2009, being a fundamental aspect of the OMERACT filter [**28**].

Conclusions

This study achieves a significantly shorter time as regards execution, suggesting that a one-joint model may be more feasible than others previously described. A single joint evaluation is all that is required to avoid unnecessary and time-consuming evaluations. Further validation in a longitudinal cohorts and a review of data on responsiveness is warranted.

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