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Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study)

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Ann Rheum Dis published online January 5, 2016

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http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2015; 25(6): 837–841
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DOI: 10.3109/14397595.2015.1040226

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ORIGINAL ARTICLE

Automated Breast Volume Scanner, a new automated ultrasonic device, is useful to examine joint injuries in patients with rheumatoid arthritis

Shin-ya Kawashiri[1,2], Takahisa Suzuki[1], Ayako Nishino[1], Yoshikazu Nakashima[1], Yoshiro Horai[1], Naoki Iwamoto[1], Kunihiro Ichinose[1], Mami Tamai[1], Hideki Nakamura[1], Tomoki Origuchi[3], Ichiro Isomoto[4], Masataka Uetani[4], Kiyoshi Aoyagi[2], and Atsushi Kawakami[1]

[1]*Departments of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan,* [2]*Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan,* [3]*Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, and* [4]*Radiological Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

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Abstract

Objective. To explore the clinical application of automated scanning of wrist and finger joints by an Automated Breast Volume Scanner (ABVS) in patients with rheumatoid arthritis (RA).
Methods. A total of 140 metacarpophalangeal (MCP) joints and 28 wrist joints from the 14 active RA patients were examined by both an ABVS system (the ACUSON S2000) from dorsal sites and by conventional ultrasonography (US) from multiple directions on the same day. We used a semiquantitative scale from 0 to 3 of synovial hypertrophy and the presence of bone erosion by grayscale for both methods; the efficacy of the two methods for identifying synovial hypertrophy and bone erosion were evaluated by kappa coefficient.
Results. The scanning time of the ABVS was 2 min per patient and that of conventional US was 15 min per patient. The kappa coefficients of synovial hypertrophy in the MCP joints were 0.60 and 0.79 in wrist joints. These values were increased in the joints where synovial hypertrophy was moderate to severe (scores greater than 2). The kappa coefficients for the presence of bone erosion in the MCP joints were 0.74 and 0.93 in wrist joints.
Conclusion. The present data showed a substantial agreement between ABVS and conventional US for assessments of the synovial hypertrophy and bone erosion of wrist and finger joints in patients with RA. Since ABVS can scan the wrist and finger joints automatically in a short time, ABVS is a helpful new ultrasonic method to examine joint injuries in patients with RA.

Abbreviations

ABVS, Automated Breast Volume Scanner; ACPA, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; JCR, Japan College of Rheumatology; MCP, metacarpophalangeal; PD, power Doppler; RA, rheumatoid arthritis; RF, rheumatoid factor; US, ultrasonography

Keywords

Automated Breast Volume Scanner, Bone erosion, Rheumatoid arthritis, Synovial hypertrophy

History

Received 18 November 2014
Accepted 6 April 2015
Published online 28 May 2015

Introduction

It is now widely accepted that ultrasound (US) is superior to clinical examination in the detection of joint inflammation [1–3]. In this issue, the European League Against Rheumatism (EULAR) task force has published its recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis (RA), and the task force stated that US is very helpful for identifying synovitis and bone erosions—and thus to making accurate diagnoses, predicting outcomes and responses to treatment, and monitoring disease progression [4]. With regard to the feasibility and appropriate training required to use US in clinical practice, problems remain: US examinations take a relatively long time and are thought to require operator-dependent techniques [4,5]. An automated US scanning system could eliminate these problems.

The ACUSON S2000™, Automated Breast Volume Scanner (ABVS) system (Siemens Medical Solutions, Mountain View, CA, USA), is a new ultrasonic device designed for the automated scanning of mammary glands. The ABVS scans mammary glands automatically in a short time [6,7]. After acquiring a series of consecutive B-mode pictures, the ABVS reconstructs three-dimensional data sets of the entire breast volume [6–8]. Here we investigated whether the ABVS system could be used for the detection of joint injuries in patients with RA. The present study was the first to explore the clinical application of the ABVS system with water immersion to detect the synovial hypertrophy and bone erosion of wrist and finger joints of RA patients compared with conventional US assessments.

Correspondence to: Dr. Shin-ya Kawashiri, Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel: +81-95-819-7067. Fax: +81-95-819-7069. E-mail: shin-ya@hotmail.co.jp

Mod Rheumatol, 2015; 25(6): 837–841

Materials and methods

Patients

Fourteen RA patients who fulfilled the 2010 RA classification criteria [9] were consecutively recruited in the present study from March to December in 2012. Each patient agreed to undergo both conventional US and ABVS as described below. They were recruited from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences. The patients gave their informed consent to be subjected to the protocol, which was approved by the Institutional Review Board of Nagasaki University.

Conventional US assessment

Conventional US was performed for each RA patient on the same day as their ABVS examination, conducted by a Japan College of Rheumatology (JCR)-certified rheumatologist (S.K.) who was blinded to the clinical and ABVS findings (S.K. is also involved in the JCR Committee for the Standardization of Musculoskeletal Ultrasonography [JCR-CoSMUS]). Images from all of the examinations were stored, and the US scoring reliability was examined in randomly selected patients at the end of the study by the three experienced rheumatologists for US including S.K. (S.K., T.S., and A.N.) who were blinded to the clinical and ABVS findings. A systematic multiplanar grayscale examination of joints was performed with the same scanner (AplioXG, Toshiba, Tokyo, Japan) using a multifrequency linear transducer (12 MHz). The bilateral 1st to 5th metacarpophalangeal (MCP) joints (dorsal recess) and wrists (intercarpal, radiocarpal, and ulnocarpal recesses) were scanned through multiple directions. All joint regions were sonographically examined in a standardized manner according to the EULAR [10] and JCR guidelines through multiple directions.

Each joint was scored for grayscale on a semiquantitative scale from 0 to 3 [11] for synovial hypertrophy as follows: Grade 0 = absence; no synovial thickening. Grade 1 = mild; minimal synovial thickening filling the angle between the periarticular bones without bulging over the line linking the tops of the bones. Grade 2 = moderate; synovial thickening bulging over the line linking the tops of the periarticular bones but without extension to at least one bone diaphysis. Grade 3 = marked; synovial thickening bulging over the line linking the tops of the periarticular bones and with extension to at least one of the bone diaphyses. The scores used in the present study were the maximum scores for grayscale obtained from any of the synovial sites evaluated at each joint. The presence or absence of bone erosion was also noted. Erosion was defined by a cortical break seen in two perpendicular planes. Interobserver agreement was evaluated by kappa coefficient via reading of captured images. Kappa coefficient of interobserver reliability of synovial hypertrophy among the three readers was 0.82–0.90 and that of bone erosion was 0.79–0.90.

ABVS assessment

The ACUSON S2000™ ABVS is an ultrasound system that automatically surveys and acquires full-field volume data. For the automatic scanning of the present patient series, we used the water immersion method with an acoustic board provided by an integrated Siemens 14L5BV linear transducer (14 MHz). Both the wrist and the finger joints were scanned by ABVS for 2 min per person in the dorsal vertical direction. The stored volume data were evaluated at a workstation. The images were evaluated in three sections: transverse, coronal, and longitudinal sections. The scores of synovial hypertrophy and the presence of bone erosion by grayscale were assessed in the same manner as described above for each joint including the bilateral wrists and the 1st to 5th MCP joints, by the same three experienced rheumatologists, who performed conventional US assessment (S.K., T.S., and A.N.), who were blinded to the clinical and conventional US findings. Both intraobserver and interobserver agreement were evaluated by kappa coefficient. Kappa coefficient of intraobserver agreement of synovial hypertrophy in each of the three readers was 0.84–0.92 and that of bone erosion was 0.77–0.86. Kappa coefficient of interobserver agreement of synovial hypertrophy among the three readers was 0.80–0.92 and that of bone erosion was 0.78–0.91.

Statistical analyses

We used the kappa coefficient to examine the associations between the ABVS assessment and the conventional US assessment of the semiquantitative scores of synovial hypertrophy and the presence of bone erosion at each site.

Results

Demographic and clinical characteristics of the 14 RA patients

The demographic and clinical characteristics of the examined RA patients are shown in Table 1. The median values of age and disease duration at examination were 55 years and 30 months, respectively. The median value of Disease Activity Score in 28 joints (DAS28)-erythrocyte sedimentation rate (ESR) was 5.81. Both rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) were positive in all 14 patients.

Joint injury found by ABVS correlated well with that found by conventional US

Representative images of synovial hypertrophy and bone erosion obtained by ABVS are provided in Figures 1–3, respectively. Our present method of water immersion with acoustic board clearly detected the synovial hypertrophy in patients with RA, as shown in Figure 1 (MCP joint) and Figure 2 (wrist joint). In Figure 1, the grade assessed by both the ABVS and conventional US was 3, and in Figure 2, grade 3 was the conclusion of both the ABVS and conventional US assessments. In Figure 3, bone erosion was shown as a defect of the cortex of the carpal bone.

We next investigated the correlations of the ABVS images with the conventional US images. Table 2 shows the semiquantitative scores of synovial hypertrophy by grayscale obtained using each method. The scores were fairly consistent for the MCP joints and wrist joints: the kappa coefficients were 0.60 for the MCP joints and 0.79 for the wrist joints.

Grade 1 grayscale synovial hypertrophy is considered equivocal compared with that of grades 2 and higher [12–14], and thus we defined grayscale synovial hypertrophy as "grayscale grade ≥ 2"

Table 1. Demographic and clinical characteristics of 14 RA patients.

	$n = 14$
Age (years[a])	55 (31–81)
Gender (Female/Male)	11/3
Duration of disease (months[a])	30 (1–240)
Positivity of RF (%)	100
Positivity of ACPA (%)	100
CRP (mg/dL[a])	1.11 (0.07–9.14)
ESR (mm/h[a])	56 (12–85)
DAS28-ESR	5.81 (3.09–8.58)
Conventional DMARDs therapy (*n*)	6 (MTX; 5, TAC; 1)
Biologics therapy (*n*)	0
Concomitant corticosteroid (*n*)	0

RF rheumatoid factor, *ACPA* anti-cyclic citrullinated peptide antibody, *DMARDs* disease-modifying antirheumatic drugs, *MTX* methotrexate, *TAC* tacrolimus.
[a]Median (range).

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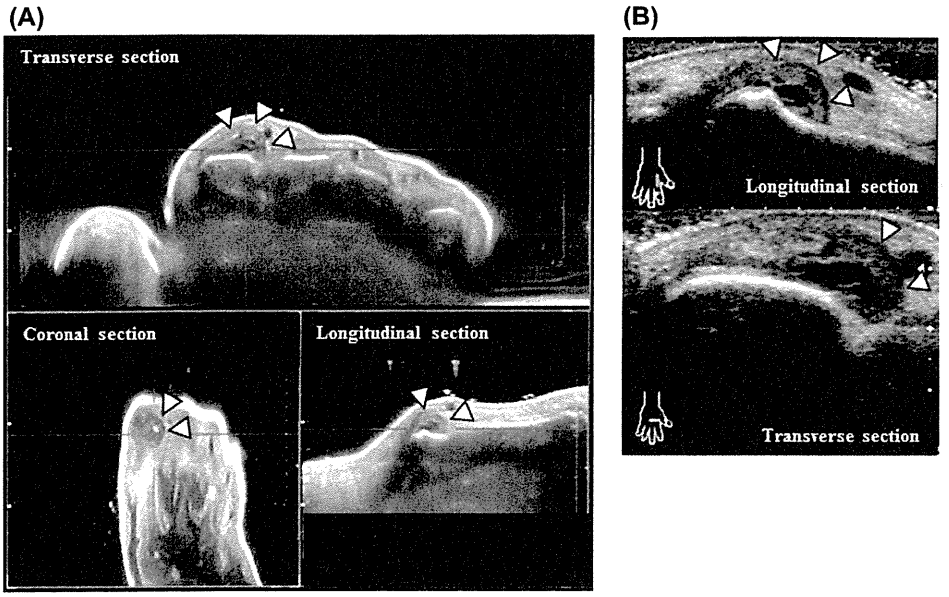

Figure 1. Synovial hypertrophy of an RA patient's 2nd MCP joint. The thickened synovium expands to the proximal ulnar side from the 2nd MCP joint (arrowhead). (A) ABVS. (B) Conventional US.

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and reevaluated the kappa coefficients. In this situation, the ABVS detected synovial hypertrophy in 22 MCP joints and 19 wrist joints, whereas the conventional US detected synovial hypertrophy in 21 MCP joints and 19 wrist joints. The kappa coefficients of synovial hypertrophy were 0.92 in the MCP joints and 1.00 in the wrist joints.

Regarding bone erosion, the ABVS detected bone erosion in 7 MCP joints and 13 wrist joints, whereas the conventional US detected bone erosion in 9 MCP joints and 12 wrist joints. The kappa coefficients of bone erosion were 0.74 in the MCP joints and 0.93 in the wrist joints.

Discussion

We applied the ABVS system for the first time to evaluate joint injuries in patients with RA. Although the ABVS data were taken from the dorsal approach only, and the data obtained with conventional US were taken from multiple directions, we observed three advantages of ABVS in this clinical application.

First, we found that ABVS is able to finely describe both synovial hypertrophy and bone erosion of the wrist and finger joints, same as conventional US. The kappa coefficients for both the ABVS and conventional US for both synovial hypertrophy and bone erosion are greater than 0.60, indicating that the findings obtained by ABVS correlate well with those by conventional US. In particular, their associations were excellent in the joints where synovial hypertrophy was moderate to severe (grade 2–3). Since the treatment decisions regarding RA are more important in active patients than inactive patients, the excellent agreement of ABVS with conventional US in this setting is an important point for clinical applications of ABVS. Therefore, the differences between ABVS and conventional US regarding the joints of GS scales 0 or 1 may not result in a critical problem in clinical practice.

Second, the use of ABVS saved scanning time. Even though the conventional US assessments in the present study were performed by a JCR-certified rheumatologist experienced in musculoskeletal US, 15 min was still necessary to accomplish the US scanning of both the wrist and finger joints in a single patient, whereas the ABVS scanned the same areas in only 2 min.

Third, ABVS was able to scan the joints automatically, providing consistent and identically filmed US images irrespective of the examiners. Furthermore, the stored volume data can be reconstructed and retrospectively evaluated at a workstation. This advantage overcomes a weak point of conventional US; that is, a time-consuming training process is necessary.

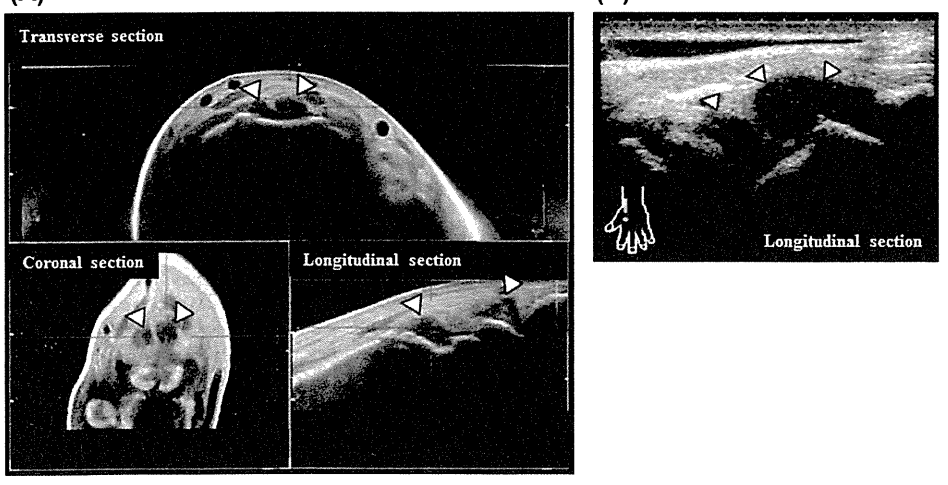

Figure 2. Synovial hypertrophy of an RA patient's wrist joint. The synovium is thickened in the radiocarpal and intercarpal joints (arrowhead). (A) ABVS. (B) Conventional ultrasonography.

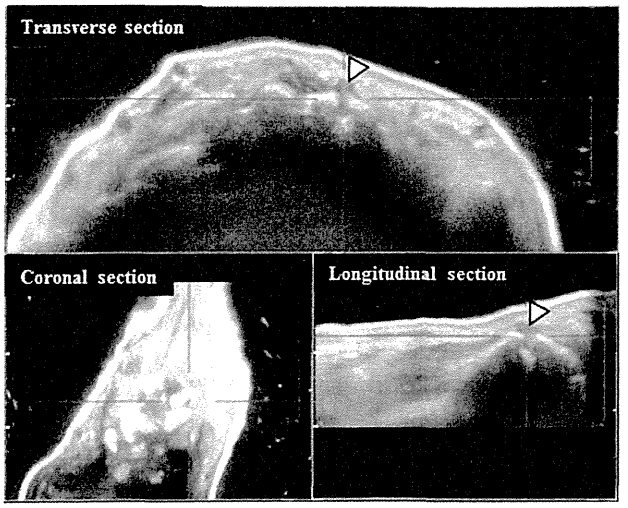

Figure 3. Bone erosion of the carpal bone. The ABVS images show a defect of the cortex of the carpal bone (arrowhead).

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However, ABVS has some disadvantages. First, the method of water immersion with an acoustical board is necessary to use ABVS. Second, at present, the evaluation of joints by power Doppler (PD) is not achieved by ABVS. Although grayscale synovitis, that is, synovial hypertrophy, is clinically meaningful for making a diagnosis, predicting the outcome, and predicting the response to treatment, the synovial PD activity is a more definitive finding than grayscale synovial hypertrophy [4,12,13,15,16]. Therefore, some modifications including the use of a contrast agent or new systems controlling the artifacts such as motion artifact are likely necessary to evaluate synovial vascularity with ABVS. Third, we did not determine whether ABVS performs well for sites other than the wrist and finger joints. Although the wrist and finger joints are the most important sites to be examined in RA patients, sites such as the knee joints, ankle joints, and metatarsopharangeal joints might need to be examined in some RA patients. The application of ABVS to varying joints is thus being investigated. Fourth, since ABVS is not able to examine the joints through multiple directions, the resolution ability of ABVS, especially in case of small joints as MCP joints or mild degree synovial hypertrophy (grade 0–1) might be a bit inferior to conventional US. The artifacts such as anisotropy, which are detected on the certain sections, can be corrected by conventional US though manual manner but not by ABVS. These differences might associate with the relatively low kappa coefficient in synovial hypertrophy of MCP joints.

In summary, we have shown that ABVS is a useful method for detecting both synovial hypertrophy and bone erosion in patients with RA. Since the sample size of the present study is relatively small (168 joints from 14 patients), validation studies with larger numbers of patients are warranted.

Table 2. Reproducibility of evaluation: conventional US and ABVS.

A. Synovial hypertrophy					
	ABVS				
	Grade 0	Grade 1	Grade 2	Grade 3	Total
MCP joints					
Conventional ultrasonography					
Grade 0	97	14	1	0	112
Grade 1	2	4	1	0	7
Grade 2	1	0	6	0	7
Grade 3	0	0	4	10	14
Total	100	18	12	10	140
Kappa coefficient	0.60				
Wrist joints					
Conventional ultrasonography					
Grade 0	4	0	0	0	4
Grade 1	3	2	0	0	5
Grade 2	0	0	13	1	14
Grade 3	0	0	0	5	5
Total	7	2	13	6	28
Kappa coefficient	0.79				

B. Bone erosion			
	ABVS		
	(+)	(−)	Total
MCP joints			
Conventional ultrasonography			
(+)	6	3	9
(−)	1	130	131
Total	7	133	140
Kappa coefficient	0.74		
Wrist joints			
Conventional ultrasonography			
(+)	12	0	12
(−)	1	15	16
Total	13	15	28
Kappa coefficient	0.93		

ABVS Automated Breast Volume Scanner, *MCP* metacarpophalangeal.

Conflict of interest

None.

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ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2015; 25(6): 948–953
© 2013 Japan College of Rheumatology
DOI: 10.3109/14397595.2013.844394

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CASE REPORT

Confirmation of effectiveness of tocilizumab by ultrasonography and magnetic resonance imaging in biologic agent-naïve early-stage rheumatoid arthritis patients

Shin-Ya Kawashiri[1,2], Takahisa Suzuki[1], Yoshikazu Nakashima[1], Yoshiro Horai[1], Akitomo Okada[1], Naoki Iwamoto[1], Kunihiro Ichinose[1], Mami Tamai[3], Kazuhiko Arima[2], Hideki Nakamura[1], Tomoki Origuchi[4], Masataka Uetani[5], Kiyoshi Aoyagi[2], and Atsushi Kawakami[1]

[1]*Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan,* [2]*Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan,* [3]*Center for Health & Community Medicine, Nagasaki University, Nagasaki, Japan,* [4]*Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, and* [5]*Department of Radiological Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

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Abstract

Efficacy of tocilizumab in active early-stage RA patients despite methotrexate was evaluated for 12 months. One out of 5 patients was quitted by infusion reaction whereas tocilizumab continued for 12 months in the remaining 4 patients. Power Doppler articular synovitis was reduced in every patient and disappeared in 2 patients. Marked MRI osteitis, found in 1 patient, had disappeared at 12 months. Present results confirm the efficacy of tocilizumab by ultrasonography and MRI.

Abbreviations

ACPA: anti-cyclic citrullinated peptide antibodies; ACR: American College of Rheumatology; CDAI: clinical disease activity index; CRP: C-reactive protein; DAS: disease activity score; DMARDs: disease-modifying antirheumatic drugs; EGA: evaluator global assessment; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GS: gray scale; IL-6: interleukin-6; IP: interpharangeal; JCR: Japan College of Rheumatology; MCP: metacarpophalangeal; mHAQ: modified Health Assessment Questionnarie Disability; mTSS: modified total Sharp score; MMP-3: matrix metalloproteinase-3; MRI: magnetic resonance imaging; MTX: methotrexate; PD: power Doppler; PIP: proximal interpharangeal; PtGA: patient global assessment; QOL: quality of life; RA: rheumatoid arthritis; RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging score; RF: rheumatoid factor; SJC: swollen joint count; TJC: tender joint count; TNF: tumor necrosis factor; US: ultrasonography

Keywords

Magnetic resonance imaging, Rheumatoid arthritis, Remission, Tocilizumab, Ultrasonography

History

Received 8 May 2013
Accepted 14 August 2013
Published online 11 November 2013

Introduction

Tocilizumab (TCZ) is a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody that blocks IL-6 from binding to its receptor. The efficacy of TCZ has been assessed in several different patient groups, and it has been shown to improve the signs and symptoms of rheumatoid arthritis (RA) patients, to suppress the radiographic progression of their joint damage, and to improve their quality of life (QOL) and physical disability [1]. As compared with TNF inhibitors, TCZ is effective to active RA patients refractory to methotrexate (MTX) even in the absence of concomitant MTX [1–3].

Recently, in addition to plain radiographs, ultrasonography (US) as well as magnetic resonance imaging (MRI) has become important in evaluating the efficacy of anti-rheumatic therapies [4,5]. The presence of either articular synovitis determined by power Doppler US (PDUS) and gray-scale US (GSUS) or osteitis by MRI is a good indicator for further structural damage [6,7]. It has been evident that TCZ efficiently protects against structural damage in patient with RA evaluated by plain radiographs [8]; however, there are few reports studying the efficacy of TCZ by US and MRI [9,10]. Recently, one Japanese regional post-marketing surveillance study found that TCZ is more effective in early-stage RA patients than in those with long-standing RA [11].

We used US and MRI to examine the effectiveness of TCZ toward active early-stage RA patients who were naïve to biologic agents despite MTX, in a small case series.

Materials and methods

Patients

From March 2011 to September 2011 we consecutively enrolled active early-stage RA patients who were naïve to biologic agents despite MTX and whose disease duration was shorter than 3 years. We enrolled 5 patients and all of the patients

Correspondence to: Shin-ya Kawashiri, M.D., Ph.D., Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel: +81-95-819-7067. Fax: +81-95-819-7069. E-mail: shin-ya@hotmail.co.jp

Table 1. Demographic and clinical characteristics at baseline of 4 RA patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	55	51	35	47	34
Gender	Female	Female	Female	Female	Female
Disease durations (months)	35	7	16	20	5
Durations to initiation of DMARDs therapy (months)	5	8	5	3	2
Steinblocker classification: stage/class	II/1	I/2	II/2	II/2	II/ 2
RF; U/ml	23.1	160.7	75.5	28.7	42.3
ACPA; U/ml	9.1	11.4	>100	19.7	0.3
Concomitant DMARD use	MTX 8 mg/wk	–	–	MTX 8 mg/wk	MTX 8 mg/wk
Tender joint count	3	6	4	5	15
Swollen joint count	4	5	4	6	10
Patient's global assessment (mm)	25	50	5	90	76
Evaluator's global assessment (mm)	23	50	15	85	78
ESR (mm/hr[a])	15	7	9	43	8
CRP (mg/dl[a])	0.02	0.01	0.12	1.04	0.03
DAS28-ESR	3.78	4.06	3.29	5.83	5.74
CDAI	11.8	21.0	10.0	28.5	40.4
SDAI	11.8	21.0	10.1	29.5	40.4
mHAQ	0.25	0.88	0.71	0.88	2.5
mTSS	5	1	12	8	0

RF, rheumatoid factor; ACPA, anti-CCP antibody; DAS28, disease activity score 28; CDAI, clinical disease activity index; SDAI, simplified disease activity index; mHAQ, modified health assessment questionnaire; mTSS, modified total Sharp score; MTX, methotrexate.

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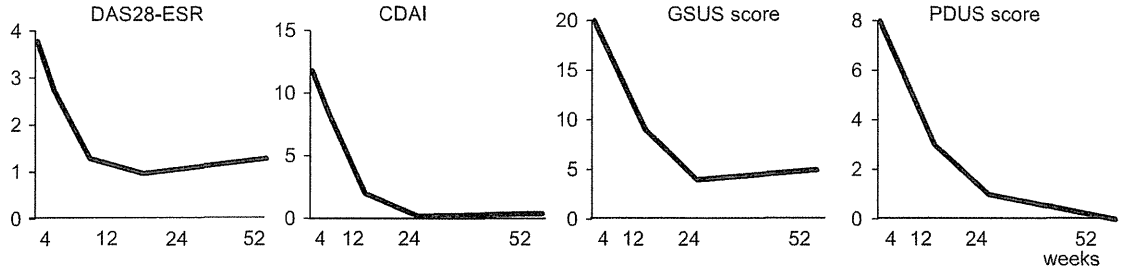
fulfilled the 2010 criteria of the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) for RA. They received 8 mg/kg of TCZ intravenously once a month for 12 months. Patients gave their informed consent to be subjected to the protocol, which was approved by the Institutional Review Board of Nagasaki University. One patient, described as case 5 in table 1, discontinued TCZ because of an infusion reaction at the second CZ treatment;



	baseline	4 weeks	12 weeks	24 weeks	52 weeks
TJC (n/28)	3	1	0	0	0
SJC (n/28)	4	4	0	0	0
PtGA (mm)	25	16	12	0	2
EGA (mm)	23	16	8	2	2
CRP (mg/dl)	0.02	0.01	0.00	0.00	0.01
ESR (mm/hr)	15	7	5	4	6

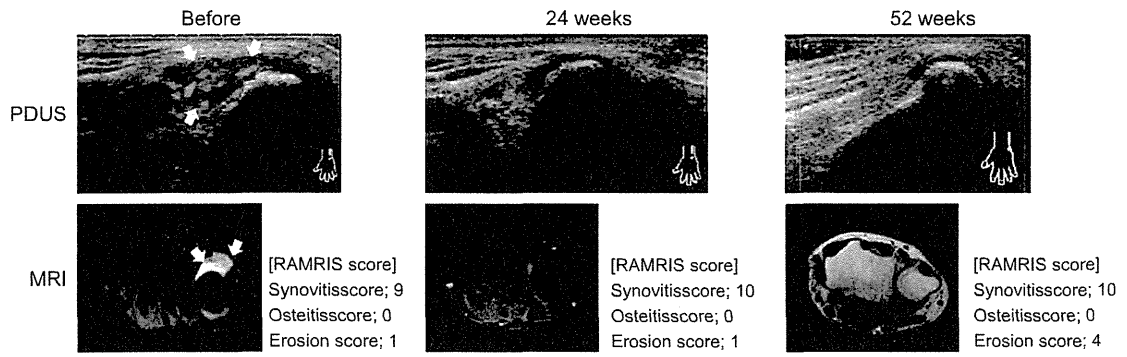


Figure 1. Improvement of clinical measures, US scores and imaging in the 12 months after induction of tocilizumab in Case 1. Thickened synovium expands from the distal radio-ulnar joint to the distal ulna at baseline. US shows power Doppler signals (grade 2) and MRI short time inversion recovery (STIR) shows high intensity in thickened synovium. These abnormal findings disappeared at 52 weeks after introduction of TCZ. The images of US show the distal ulna of left hand (longitudinal scan and dorsal aspect). The images of MRI show the distal radio-ulnar joint of left hand (transverse section). CDAI, clinical disease activity index; CRP, C-reactive protein; DAS, disease activity score; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; GSUS, gray-scale ultrasonography; MRI, magnetic resonance imaging; PDUS, power Doppler ultrasonography; PtGA, patient global assessment; TJC, tender joint count; SJC: swollen joint count.

however, the other 4 patients successfully continued TCZ for 12 months.

Clinical and imaging assessment

The clinical response to therapy was evaluated using disease activity score (DAS) 28, clinical disease activity index (CDAI), modified Health Assessment Questionnaire Disability (mHAQ) and a Boolean approach every 12 weeks by Japan College of Rheumatology (JCR)-certified rheumatologists (H.N. and A.K.) who were blinded to the findings of US, MRI and plain radiographs.

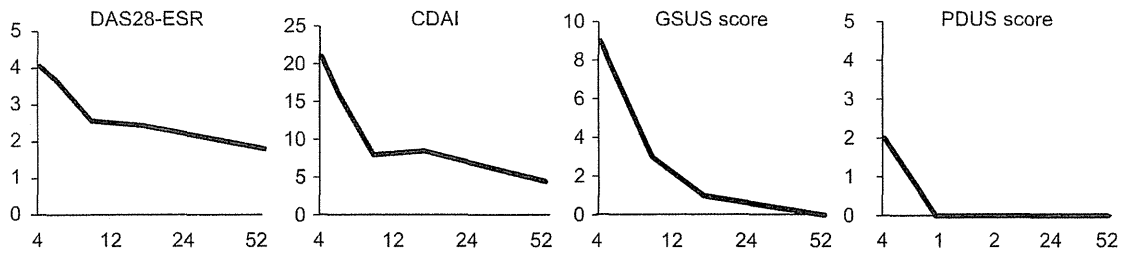
Ultrasonography was performed at baseline and at 3, 6 and 12 months on the same day as the clinical evaluation by a JCR-certified rheumatologist (S.K.) who was blinded to the clinical findings (S.K. is also a experienced of MSKUS examiner; 7 years experience of MSKUS). A systematic multiplanar GS and PD examination of 22 joints was performed with the same scanner (TOSHIBA AplioXG) using a multifrequency linear transducer (12 MHz). The ultrasound score included the following 22 joints: bilateral wrists (intercarpal, radiocarpal and ulnocarpal recesses) and finger joints including the 1st – 5th metacarpophalangeal (MCP) joints, the 1st interphalangeal (IP) joint and the 2nd – 5th proximal interphalangeal (PIP) joints (dorsal recess). All joint regions were sonographically examined in a standardized manner according to the EULAR [12] and JCR guidelines. These scores corresponded to the maximum PD score obtained from any of the synovial sites evaluated at each joint. The sums of the PD ultrasonography (PDUS) scores obtained from each joint were used as 22j-PDUS scores (range: 0–66) and those of the GSUS scores obtained from each joint were used as 22j-GSUS scores (range: 0–66), respectively.

Plain MRI of both wrist and finger joints was performed at baseline and at 6 and 12 months as we previously described [13,14]. The severity of MRI-proven joint injury of synovitis and osteitis was evaluated by RA MRI scoring (RAMRIS) according to the standard method by an experienced radiologist who was blinded to clinical and US findings and modified total Sharp score (mTSS) (M.U).

Plain radiographs of both hands and feet were performed at baseline and at 12 months, and were evaluated by mTSS by experienced rheumatologists who were blinded to the clinical, US findings and MRI findings (A.O. and Y.H.).

Results

The demographic and clinical characteristics of the 4 RA patients treated with TCZ are shown in Table 1. Five patients were enrolled. Although one patient (case 5 in table 1) was withdrawn because of an infusion reaction at the second TCZ treatment, the remaining 4 patients were successfully treated with TCZ for 12 months. The baseline variables are described in Table 1. As shown in Table 1, all of the patients were



	baseline	4 weeks	12 weeks	24 weeks	52 weeks
TJC (n/28)	6	5	3	1	0
SJC (n/28)	5	5	1	1	0
PtGA (mm)	50	30	25	45	40
EGA (mm)	50	30	15	15	5
CRP (mg/dl)	0.01	0.00	0.01	0.01	0.01
ESR (mm/hr)	7	7	4	4	6

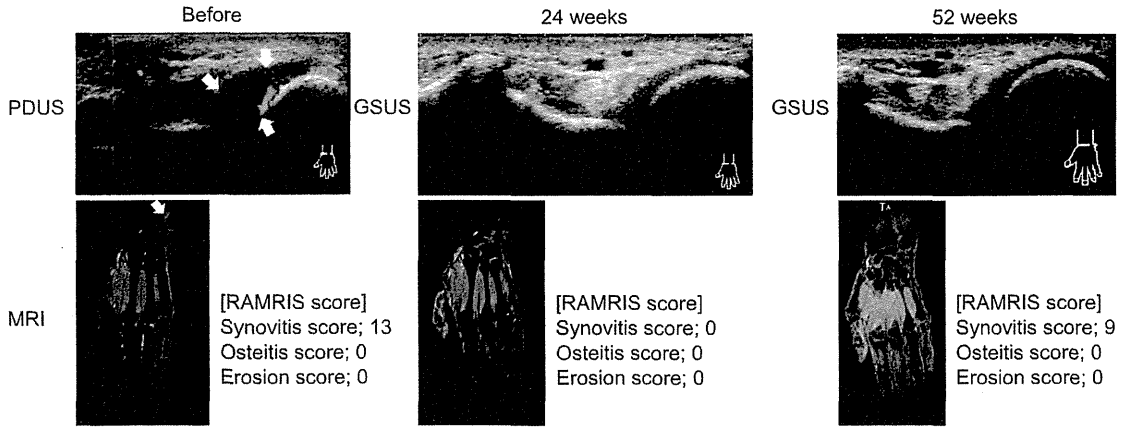


Figure 2. Improvement of clinical measures, US scores and imaging in the 12 months after induction of tocilizumab in Case 2. Thickened synovium expands from the distal radio-ulnar joint to the distal ulna at baseline. US shows power Doppler signals (grade 2) and MRI short time inversion recovery (STIR) shows high intensity in thickened synovium. These abnormal findings disappeared at 52 weeks after introduction of TCZ. The images of US show the distal ulna of left hand (transverse scan and dorsal aspect). The images of MRI show left hand (coronal section). Abbreviations are as in the Figure 1 legend. GSUS, gray scale ultrasonography.

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double positive with anti-cyclic citrullinated peptide antibodies (ACPA) or rheumatoid factor (RF) and had experienced at least 3 months of moderate or high disease activity determined by DAS28 despite early initiation with MTX treatment. Since the officially approved maximum weekly dosage of MTX in Japan was only recently extended to 16 mg at March 2011 from 8 mg, all of the patients in the present study received 8 mg per week of MTX. All of the 5 patients were positive with autoantibodies, therefore, an introduction of biologic DMARDs was considered. This was an open-labeled observational study. A recent randomized controlled trial revealed the similar efficacy of TCZ in the presence or absence of MTX [2] and TCZ monotherapy is stated as effective and is not significantly inferior to combination therapy with MTX as compared with TNF inhibitors [3]; thus, the continuation of MTX after TCZ was dependent on the patient's decision after discussion with physicians. Case 1, 4 and 5 continued MTX whereas case 2 and 3 discontinued MTX, respectively.

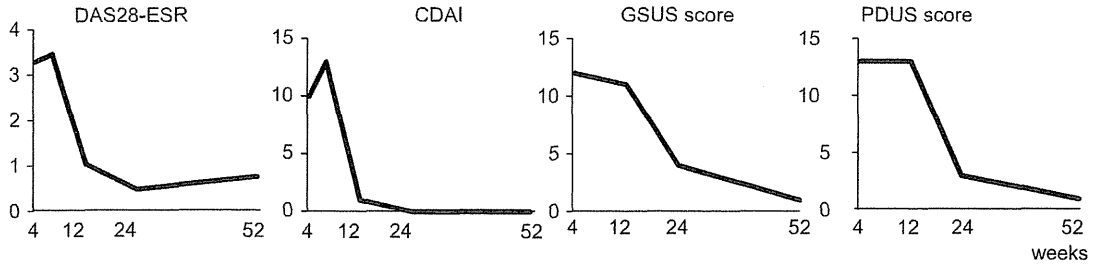
The changes of clinical measures, US images and MRI in the 12 months after induction of TCZ in case 1, 2, 3 and 4 are shown in Figures 1, 2, 3 and 4, respectively. Below, we briefly summarize their therapeutic courses.

Case 1: DAS28 remission was achieved at 3 months. Clinical disease activity score (CDAI) remission and Boolean remission appeared at 6 months. In parallel to clinical improvement, US scores also decreased. PDUS score disappeared at 12 months whereas GSUS score remained at 6 points at 12 months. There was no plain radiographic progression at 12 months (ΔmTSS was 0) though RAMRIS bone erosion score was increased from 1 to 4 during the treatment at the left wrist joints where remarkable PD synovitis was detected at entry (Figure 1).

Case 2: DAS28 remission was achieved at 12 months whereas CDAI remission as well as Boolean remission was not achieved because of the remainder of the patient's global assessment. The US score was also improved, and the PDUS score as well as the GSUS score was zero at 12 months. There was no plain radiographic progression at 12 months (ΔmTSS was 0). This case showed a discrepancy between clinical evaluation and the improvement of imaging. She remained to complain symptoms other than joint, such as fatigue.

Case 3: DAS28 remission, CDAI remission and Boolean remission were achieved at 3 months. US score was also improved in parallel to clinical assessment whereas 1 point remained at 12 months in both the PDUS and GSUS scores. There was no plain radiographic progression at 12 months (ΔmTSS was 0).

Case 4: Baseline clinical disease activity was high as compared with the remaining 3 patients and the marked MRI osteitis was only found at entry. PDUS score at baseline was 3 at right wrist joint and 2 at left wrist joint, respectively. DAS28 remission was achieved at 1 month and CDAI remission as well as Boolean



	baseline	4 weeks	12 weeks	24 weeks	52 weeks
TJC (n/28)	4	7	0	0	0
SJC (n/28)	4	4	0	0	0
PtGA (mm)	5	12	5	0	0
EGA (mm)	15	8	5	0	0
CRP (mg/dl)	0.12	0.04	0.01	0.01	0.01
ESR (mm/hr)	43	7	7	6	3

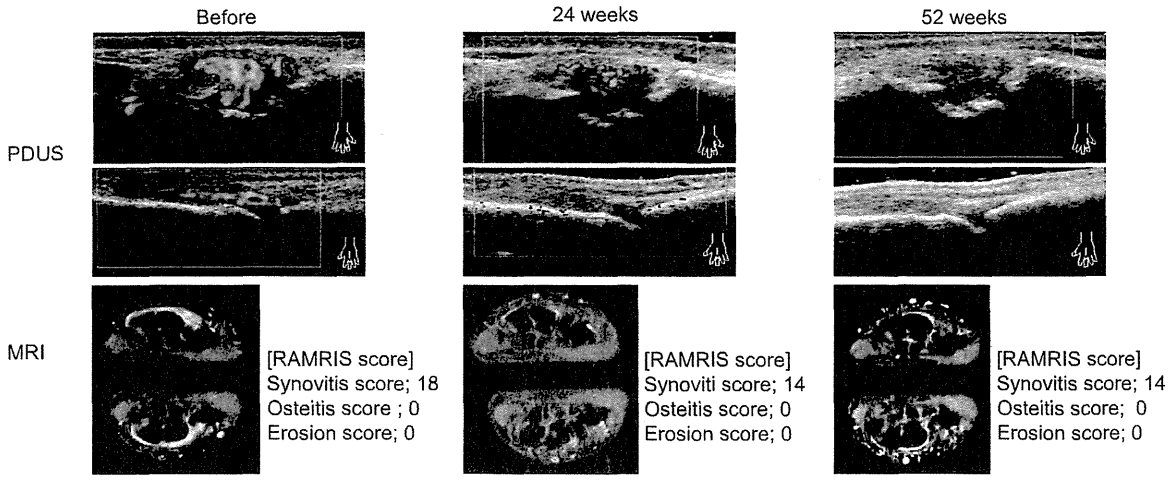


Figure 3. Improvement of clinical measures, US scores and imaging in the 12 months after induction of tocilizumab in Case 3. The upper images of US show the 2nd MCP joint of right hand (longitudinal scan and dorsal-radial aspect). Power Doppler grade 3 synovitis with bone erosion at baseline improved after introduction of TCZ (Power Doppler grade 2 at 24 weeks and grade 1 at 52 weeks). The lower images of US show the 3rd MCP joint of left hand (longitudinal scan and dorsal aspect). Power Doppler grade 3 synovitis at baseline disappeared in 24 weeks after introduction of TCZ. The images of MRI show the wrist joints of bilateral hands (transverse section) shows high intensity in thickened synovium on MRI short time inversion recovery (STIR) at baseline improved after introduction of TCZ. Abbreviations are as in the Figure 1 legend.

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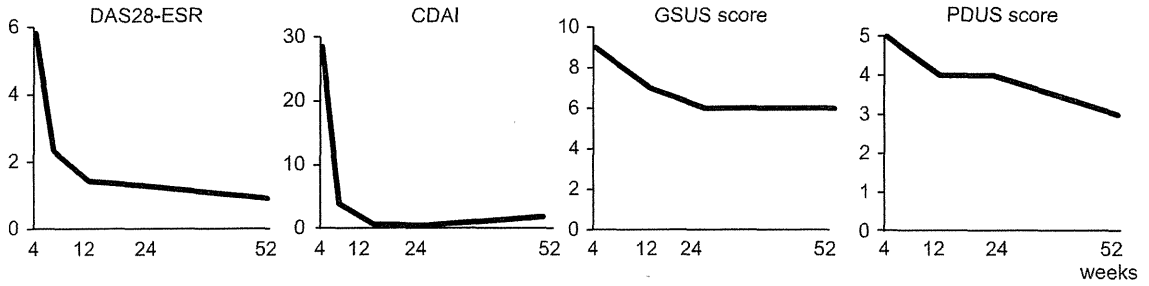

	baseline	4 weeks	12 weeks	24 weeks	52 weeks
TJC (n/28)	5	1	0	0	0
SJC (n/28)	6	1	0	0	0
PtGA (mm)	90	10	5	3	10
EGA (mm)	85	10	3	3	10
CRP (mg/dl)	1.04	0.01	0.01	0.01	0.01
ESR (mm/hr)	43	7	7	6	3

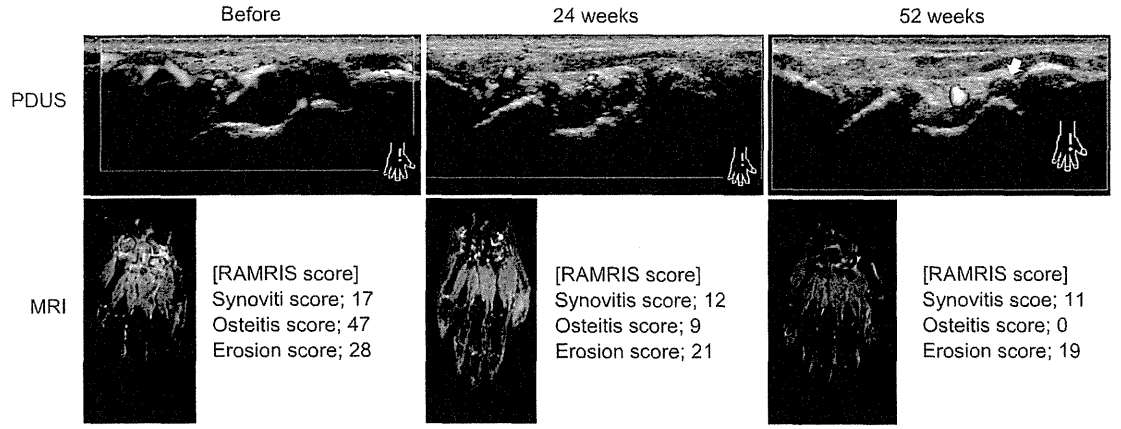

Figure 4. Improvement of clinical measures, US scores and imaging in the 12 months after induction of tocilizumab in Case 4. The images of US show the wrist joint of right hand (longitudinal scan and dorsal-radial aspect). Power Doppler grade 3 synovitis at baseline improved after introduction of TCZ (Power Doppler grade 2 at 24 weeks and grade 1 (arrow) at 52 weeks). The images of MRI show the right hands (coronal section) shows remarkable synovitis and osteitis as high intensity on MRI short time inversion recovery (STIR) at baseline disappeared at 52 weeks after introduction of TCZ. Abbreviations are as in the Figure 1 legend.

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remission appeared at 3 months. US score was also decreased, but still remained at 12 months (PDUS sore; 3, GSUS score; 6, respectively). MRI osteitis score also improved and disappeared at 12 months. There was slight plain radiographic progression of joint space narrowing at 12 months of right wrist joints where both PD synovitis and MRI osteitis were remarkable at entry (ΔmTSS was 1).

All 4 patients achieved mHAQ remission at 12 months: Case 1, 0; Case 2, 0.1; Case 3, 0 and Case 4, 0. MRI synovitis was found in all patients; however, its improvement was not as significant as that of the US score.

Discussion

Although this is a small case report, the present investigation is the first to examine the efficacy of TCZ in active early-stage RA despite MTX treatment by clinical measures as well as US and MRI. All patients who continued with TCZ achieved remission of DAS28 and mHAQ. In addition, three out the 4 patients achieved both CDAI and Boolean remission. Previous reports have found that high radiographic damage at the baseline predicts a poor prognosis in patients with RA [15]. In fact, Japanese regional post-marketing surveillance of etanercept-treated RA patients has found that higher HAQ and mTSS at baseline disturbs the improvement of physical disability at 1 year, and the cutoff point necessary for mTSS at baseline toward HAQ remission is 55.5 [16]. Since the maximum mTSS at baseline was 12, the clinical efficacy of the present study appears to be excellent. In addition to the clinical data, we have found an interesting insight obtained by US and MRI.

According to the results of Haarvardsholm et al. in dominant wrist joints from 36 RA patients treated by TNF inhibitors, the RAMRIS synovitis score is more highly responsive to therapies than US measurements [17]. US was evaluated in that study as the total US inflammatory score combining GS articular synovitis, GS tenosynovitis and synovial fluid; GS articular synovitis alone or PD articular synovitis alone was not examined [17]. PD articular synovitis and GS articular synovitis are suggested to reflect synovial inflammation more precisely than tenosynovitis and synovial fluid [18]. Additionally, since the present study included a broader area than Haarvardsholm et al., observing both wrist joints, MCP joints and PIP joints by PD articular synovitis and GS articular synovitis, our US measurements appears to be to be more responsive than those of Haarvardsholm et al. [17]. Although the qualification of synovitis by plain MRI was less sensitive than that by gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI [13], our data showed that US measurements of PD articular synovitis and GS articular synovitis were more responsive to the disease activity of RA than the RAMRIS synovitis score. The PD articular synovitis score appeared to be more responsive than the GS articular synovitis score in the present study, that is assumed by the other accumulated observations [3].

Synovitis determined by US tends to remain in spite of the achievement of clinical remission [6]. In the present study, two out of 4 patients achieved PDUS remission. The PDUS score of the other cases was also as low as 1 or 2 at 12 months, indicating that the efficacy of TCZ is confirmed by US measurements. The course of MRI osteitis is similar to US synovitis [14]. Our present data showed a disappearance of the marked MRI osteitis by TCZ. TCZ's significant inhibition of joint destruction in patients with RA has previously been shown [1,8]; and the present data confirms that effect, emphasizing that TCZ directly suppresses the inflammatory responses of synovial tissues and adjacent bone, eliciting a protecting effect toward rheumatoid joints. These effects were achieved in the absence of MTX in the ACT-RAY study [2].

This is a small study of 4 cases; however, we have precisely examined the patients' courses by clinical, US and MRI measurements. Information of the effectiveness of TCZ examined by MRI and US are limited [9,10], however, we have found that TCZ really improves the rheumatoid synovial inflammation. Since each joint area interested is different in physical examination, US, MRI and plain radiograph, further studies focusing on the exact areas are necessary. In conclusion, although there are some limitations describe above, TCZ demonstrated an excellent effect in RA patients who were naïve to biological agents refractory to MTX by inhibiting synovial inflammatory responses.

Acknowledgements

We thank Prof. Masataka Uetani (Department of Radiology and Radiation Research, Nagasaki University Graduate School of Biomedical Sciences) for assistance with RAMRIS. We also thank Dr. Akitomo Okada and Dr. Yoshiro Horai (Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences) for performing mTSS. The part of this study was supported by Abbvie GK, Astellas Pharma Inc., Chugai Pharmaceutical Co., Eisai Co., Eli Lilly Japan, Janssen Pharmaceutical K. K., Mitsubishi Tanabe Pharma Co., Otsuka Pharmaceutical Co., Pfizer Japan, Santen Pharmaceutical Co, Ltd, Takeda Pharmaceutical Company, Taisho Toyama Pharmaceutical Co.

Conflict of interest

None.

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Upregulation of Thrombospondin 1 Expression in Synovial Tissues and Plasma of Rheumatoid Arthritis: Role of Transforming Growth Factor-β1 toward Fibroblast-like Synovial Cells

Takahisa Suzuki, Naoki Iwamoto, Satoshi Yamasaki, Ayako Nishino, Yoshikazu Nakashima, Yoshiro Horai, Shin-ya Kawashiri, Kunihiro Ichinose, Kazuhiko Arima, Mami Tamai, Hideki Nakamura, Tomoki Origuchi, Chikara Miyamoto, Makoto Osaki, Kaname Ohyama, Naotaka Kuroda, and Atsushi Kawakami

ABSTRACT. ***Objective.*** To investigate the role of thrombospondin 1 (TSP-1) in RA.

Methods. Expression of TSP-1 in synovial tissues was determined by immunohistochemistry. Expression of TSP-1 in rheumatoid fibroblast-like synovial cells (FLS) was investigated by quantitative real-time PCR and ELISA. Correlations among the plasma TSP-1 and other variables in patients with RA were examined.

Results. Expression of TSP-1 was increased in rheumatoid synovial tissues. Transforming growth factor-β1 (TGF-β1) clearly increased TSP-1 expression in FLS on both mRNA and protein levels. Changes in plasma TSP-1 were associated with those in 28-joint Disease Activity Score-erythrocyte sedimentation rate and plasma TGF-β1.

Conclusion. TSP-1 might be critically involved in the disease process of RA through the TGF-β1/TSP-1 axis. (First Release May 1 2015; J Rheumatol 2015;42:943–7; doi:10.3899/jrheum.141292)

Key Indexing Terms:
RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIAL CELL SYNOVITIS
THROMBOSPONDIN 1 TRANSFORMING GROWTH FACTOR-B1 BIOMARKER

Our recent investigations using circulating immune complexes (CIC) analysis revealed that CIC-associated thrombospondin 1 (TSP-1) is frequently found in the serum of rheumatoid arthritis (RA), but not in other rheumatic diseases and healthy controls[1]. TSP-1 is a multifunctional glycoprotein expressed in cells from multiple lineages[2]. Although the role of TSP-1 in inflammation remains obscure, studies have shown that TSP-1 acts as a proinflammatory protein. For example, TSP-1 binds to specific receptors on polymorphonuclear leukocytes and stimulates their motility[3]. One study showed that TSP-1 activates the macrophages through the Toll-like receptor 4 pathway[4].

In our present study, to establish the role of TSP-1 in RA both *in vitro* and in clinical practice, we used 3 approaches. First, we investigated the expression of TSP-1 in synovial tissues. Second, we investigated whether the expression of

From the Department of Immunology and Rheumatology, Department of Public Health, Department of Health Sciences, Department of Orthopedic Surgery, and Department of Environmental and Pharmaceutical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki; and Department of Clinical Immunology and Rheumatology, Hiroshima University, Hiroshima, Japan.

Supported in part by a grant from the Ministry of Health, Labor, and Welfare, Japan.

T. Suzuki, MD; N. Iwamoto, MD, PhD, Assistant Professor, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences; S. Yamasaki, MD, PhD, Department of Clinical Immunology and Rheumatology, Hiroshima University; A. Nishino, MD; Y. Nakashima, MD; Y. Horai, MD, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences; S.Y. Kawashiri, MD, PhD, Department of Immunology and Rheumatology, and Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences; K. Ichinose, MD, PhD, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences; K. Arima, MD, PhD, Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences; M. Tamai, MD, PhD; H. Nakamura, MD, PhD, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences; T. Origuchi, MD, PhD, Professor, Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences; C. Miyamoto, MD, PhD; M. Osaki, MD, PhD, Professor, Department of Orthopedic Surgery, Nagasaki University Graduate School of Biomedical Sciences; K. Ohyama, PhD; N. Kuroda, PhD, Professor, Department of Environmental and Pharmaceutical Sciences, Nagasaki University Graduate School of Biomedical Sciences; A. Kawakami, MD, PhD, Professor, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences.

Address correspondence to Dr. N. Iwamoto, Assistant Professor, Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail: naoki-iwa@nagasaki-u.ac.jp

Accepted for publication February 24, 2015.

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TSP-1 in fibroblast-like synovial cells (FLS) from patients with RA was influenced by cytokines and growth factors. Finally, we analyzed the correlation between plasma levels of TSP-1 and clinical variables of RA. By using these approaches, we show that TSP-1 is, at least in part, associated with the pathogenesis of RA.

MATERIALS AND METHODS

Each patient provided a signed consent form to participate in our study, which was approved by the Institutional Review Board of Nagasaki University. All patients with RA fulfilled the classification criteria for RA[5]. We obtained synovial tissues from patients with RA or osteoarthritis (OA) at the time of orthopedic surgery. FLS from patients with RA were isolated from synovial tissues as described previously[6].

Reagents and stimulation assays. FLS were stimulated for 24 h with transforming growth factor-β1 (TGF-β1; 5 ng/ml), interleukin 1β (IL-1β; 10 ng/ml), IL-6 (100 ng/ml) with soluble IL-6 receptor (100 ng/ml), interferon-γ (IFN-γ; 10 ng/ml, all from R&D Systems), and tumor necrosis factor-α (TNF-α; 100 ng/ml, Millipore). In another subset of stimulation experiments, FLS were stimulated with various concentrations of recombinant TSP-1 (R&D Systems) for various time periods (24, 48, or 96 h).

RNA isolation and quantitative real-time PCR analysis. RNA was isolated with Trizol reagent (Life Technologies) and reverse-transcribed. Quantification of TSP-1 mRNA was performed by SYBR Green Real-Time PCR as previously described[7]. The following primers were designed: TSP-1 5′-GGA GAC AAA GAC TGG CTT CTG GAC-3′ (forward), 5′-GGC CAC TGC AGG TGA TGA GTA A-3′ (reverse); β-actin 5′-AGC CTC GCC TTT GCC GA-3′ (forward), 5′-CTG GTG CCT GGG GCG-3′ (reverse). Expression of β-actin was used as endogenous control. For relative quantification, the comparative threshold cycle method was used.

Immunohistochemistry. Synovial tissues were stained using the labeled streptavidin-biotin method. We used TSP-1 antibody at 1:25 dilution (Thermo Scientific) or with mouse IgG (Jackson ImmunoResearch Laboratories Inc.) as a negative control. Staining was visualized with diaminobenzidine using a peroxidase substrate kit, and then the area of TSP-1–positive staining was randomly quantified in 1 field per section by an imaging software as we previously described (WinROOF, Mitani Corp.)[8].

ELISA. Proteins were detected by ELISA using ELISA kits specific for TSP-1, IL-6, TGF-β1, TNF-α, and vascular endothelial growth factor (VEGF) according to the manufacturer's instructions (R&D Systems).

Clinical evaluation of the patients with RA. The present study included 16 patients with active RA (detailed characteristics of the patients, as well as additional information concerning the methodology used in these studies, are available upon request from the authors). Disease Activity Score at 28 joints (DAS28)-ESR (erythrocyte sedimentation rate) and plasma or serum concentrations of TSP-1, TGF-β1, IL-6, and VEGF were examined at baseline and after introduction of disease-modifying antirheumatic drugs (DMARD) therapy (from 3 mos to 15 mos).

Statistical analysis. GraphPad Prism software was used for statistical analysis. Normal distribution of the data was confirmed using the Kolmogorov-Smirnov test. For related data, statistical significance was evaluated by Student t test (parametric data) or by Wilcoxon signed-rank test (nonparametric data). Student t test (parametric data) or Mann-Whitney U test (nonparametric) was used for unrelated data. The strength of the correlation was judged by Spearman rank correlation coefficient. All data were expressed as the mean and SD. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Elevated expression of TSP-1 in RA synovial tissues. Pronounced expression of TSP-1 was found in the synovial lining and sublining layers in RA synovial tissues, but also perivascular areas as compared with that of patients with OA (Figure 1A). The quantification analysis using WinROOF software confirmed these results (Figure 1B).

TSP-1 production from FLS is induced by TGF-β1. Among inflammatory cytokines and growth factors, TGF-β1 most clearly increased TSP-1 expression in FLS on an mRNA level (Figure 2A). To confirm this, we analyzed the expression of TSP-1 on the protein level after stimulation with TGF-β1 by ELISA (Figure 2B). Similar to mRNA levels, TGF-β1 markedly induced TSP-1 protein, indicating that TGF-β1 stimulates TSP-1 production at both the transcriptional and protein levels. However, other stimuli, including IL-1β, did not induce TSP-1 production at the protein level [representative results for TSP-1 in the culture supernatants of each stimulated FLS were 1.45 pg/ml (TNF-α), 0.97 pg/ml (IL-1β), 2.34 pg/ml (IL-6), 1.38 pg/ml (IFN-γ), 59.73 pg/ml (TGF-β1), and control (3.46 pg/ml)].

TSP-1 did not induce production of TGF-β1, IL-6, or TNF-α. We stimulated FLS with TSP-1 for various time periods (24, 48, 96 h) and at different concentrations. TGF-β1 and TNF-α were not detected after TSP-1 stimulation. IL-6 could be detected, but not increased by TSP-1 [the representative mean values of IL-6 after TSP-1 stimulation (for 24 h) were 105.6 pg/ml (control), 107.0 pg/ml (10 ng/ml), 94.7 pg/ml (100 ng/ml), and 88.0 pg/ml (1000 ng/ml)].

Plasma levels of TSP-1 correlated with disease activity of RA. The following DMARD were used as new treatment in our study: methotrexate (12 patients), salazosulfapyridine (1 patient), etanercept (2 patients), and infliximab (1 patient). Overall, DAS28-ESR and serum VEGF (5.18 ± 1.30 and 724.8 ± 647.1 pg/ml at baseline, respectively) were significantly decreased after introduction of treatment (3.51 ± 2.03, $p < 0.05$ and 514.3 ± 411.2 pg/ml, $p < 0.05$), whereas other variables were not changed [Baseline: TSP-1 4.79 ± 5.59 μg/ml, TGF-β1 18.47 ± 8.63 pg/ml, IL-6 17.84 ± 26.01 pg/ml. After induction of new treatment: TSP-1 5.16 ± 5.49 μg/ml ($p = 0.86$), TGF-β1 15.81 ± 8.21 pg/ml ($p = 0.28$), IL-6 8.63 ± 12.04 pg/ml ($p = 0.25$)].

There was large variability in the value of each variable among each case. Therefore, we compared the amount of change. We investigated the correlations between plasma levels of TSP-1 and other variables. The result is shown in Figure 3. The changes (Δ values) in TSP-1 significantly correlated with those in DAS28-ESR. Because it was found *in vitro* that TGF-β1 stimulates the production of TSP-1 in FLS, there was a clear correlation between the ΔTSP-1 and ΔTGF-β1 during DMARD therapies. Similar correlations were found between TSP-1 and IL-6, and TSP-1 and VEGF.

DISCUSSION

In our present study, we found that TSP-1 expression in synovial tissues was much higher in RA than OA. This result is consistent with previous reports[9,10]. The published data on

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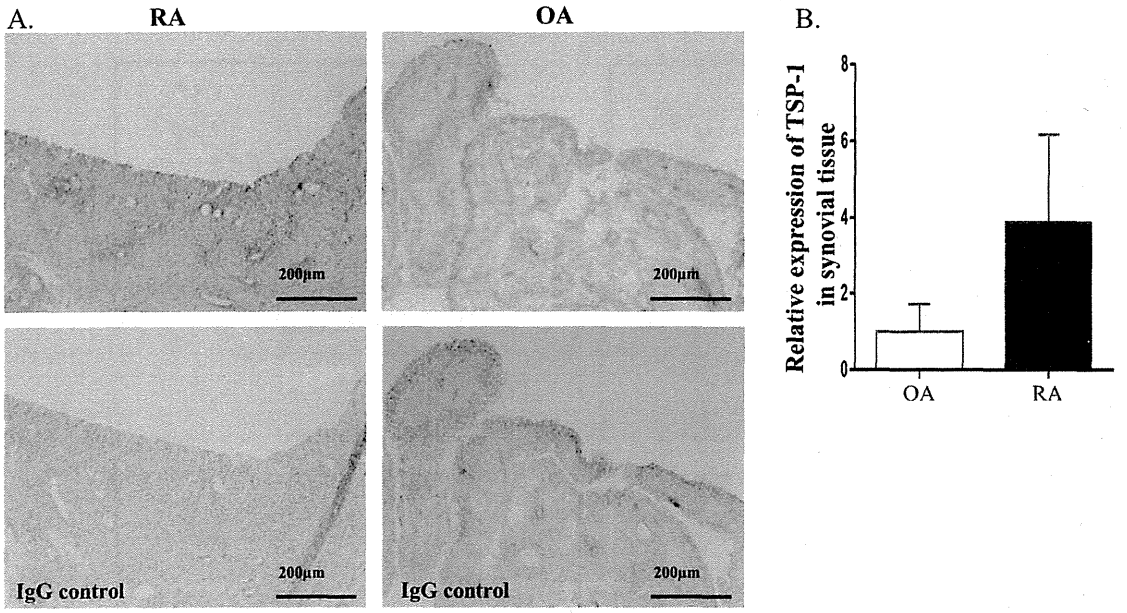

Figure 1. TSP-1 expression in synovial tissues from patients with RA and OA. A. Representative sections of synovial tissues stained for TSP-1 or control IgG. Positive staining of TSP-1 appears as a light brown color. Expression is seen in the synovial lining and sublining layers and perivascular areas. B. The quantification analysis of TSP-1 staining in RA (n = 4) and OA (n = 4) synovial tissues was performed using WinROOF software (Mitani Corp.). Expression of TSP-1 was determined relative to OA synovial tissue, which was defined as 1. Values are presented as the means. TSP-1: thrombospondin 1; RA: rheumatoid arthritis; OA: osteoarthritis; IgG: immunoglobulin G.

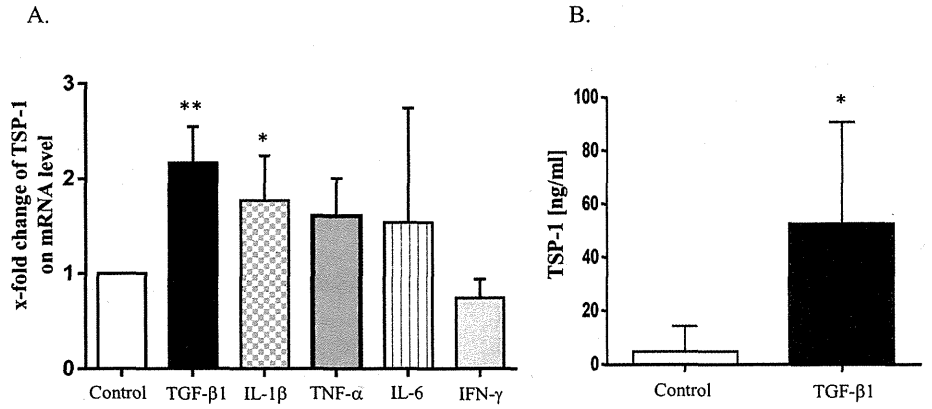

Figure 2. A. Increment of TSP-1 mRNA expression by TGF-β1. RA-FLS (n = 4) was stimulated with TGF-β1 (5 ng/ml), IL-1β (10 ng/ml), IL-6 (100 ng/ml) with soluble IL-6R (100 ng/ml), TNF-α (100 ng/ml), or IFN-γ (10 ng/ml) for 24 h. TSP-1 expression was determined by SYBR Green Real-Time PCR and was stated relative to the control, which was defined as 1. Values are presented as the means ± SD. * $p < 0.05$. ** $p < 0.01$ versus the controls (no stimulation). B. Increment of TSP-1 protein production in culture supernatants from RA-FLS by TGF-β1. RA-FLS (n = 6) was stimulated with TGF-β1 (5 ng/ml) for 24 h. TSP-1 protein production in the supernatants was examined by ELISA. Values are presented as the means ± SD. * $p < 0.05$ versus the controls (no stimulation). TSP-1: thrombospondin 1; TGF-β1: transforming growth factor-β1; RA: rheumatoid arthritis; FLS: fibroblast-like synovial cells; IL-1β: interleukin 1β; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-γ.

the effects of TSP-1 in RA and inflammation have diverged[11,12]. But considering the result that expression of TSP-1 is evident in the lining and sublining layers of rheumatoid synovial tissues where active inflammation is found, TSP-1 might be involved in rheumatoid synovitis.

Here we could show that TGF-β1 significantly augmented

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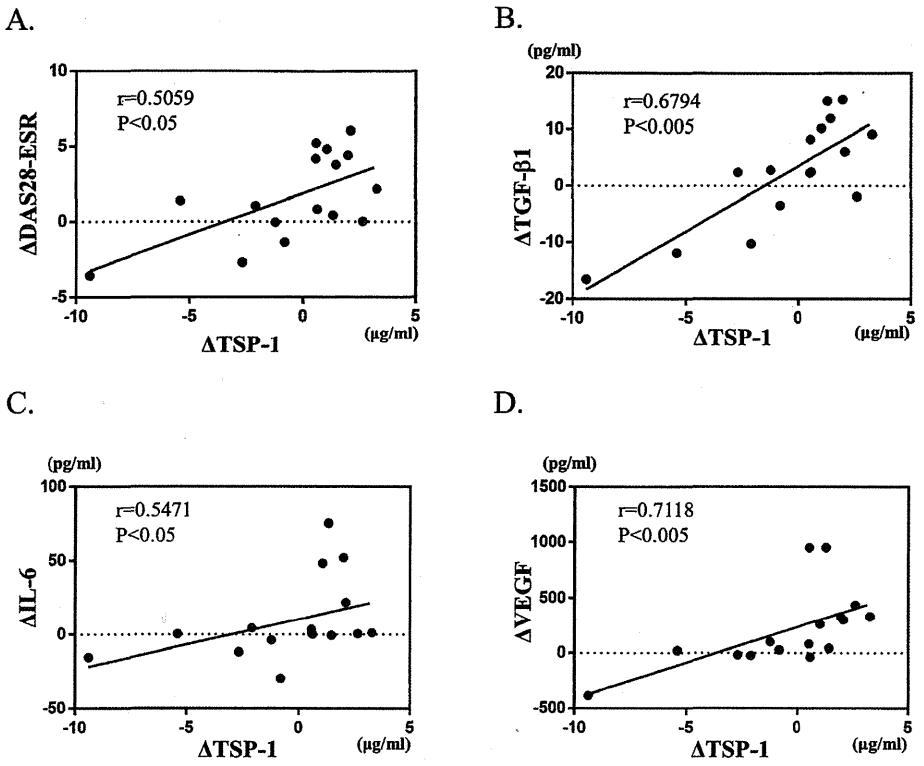

Figure 3. Correlations between Δ values in plasma TSP-1 and those in (A) DAS28-ESR, (B) plasma TGF-β1, (C) serum IL-6, and (D) serum VEGF after introduction of DMARD therapies (n = 16). The Spearman rank correlation coefficient and the corresponding p value are shown above each scatter plot. TSP-1: thrombospondin 1; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; TGF-β1: transforming growth factor-β1; IL-6: interleukin 6; VEGF: vascular endothelial growth factor; DMARD: disease-modifying antirheumatic drugs.

TSP-1 synthesis from FLS. This is the first observation to describe the role of TGF-β1 as an activator of TSP-1 in FLS. Although TGF-β1 is known as a paradoxical regulator for inflammation[13], TGF-β1 has the competence to inhibit Fas-mediated apoptosis of FLS[14], activates the pathway of nuclear factor-κB coordinating with IL-1 and TNF-α, and induces synovial lining hyperplasia[15,16]. The close interplay between TSP-1 and TGF-β1 has been well established. TSP-1 is known as an activating factor for a latent form of TGF-β1[17]. We have found that production of TSP-1 from FLS is increased by the stimulation of TGF-β1, whereas TSP-1 does not induce production of TGF-β1. Our findings suggested that TSP-1 does not directly act on cytokines and growth factors production. Further studies will be needed to better understand the role of the TGF-β1/TSP-1 axis in RA synovial tissues.

The Δ values of DAS28, plasma TGF-β1, serum IL-6, and VEGF were significantly correlated with Δplasma TSP-1. Although TSP-1 showed no interaction with IL-6 *in vitro*, Δplasma TSP-1 significantly correlated with Δserum IL-6. It might come from the effect, not through synovial tissues, or it might reflect the disease activity individually. Correlation between Δplasma TSP-1 and ΔDAS28 indicates that TSP-1 may be implicated in active RA disease and could become a novel biomarker of RA, as well as IL-6.

There are some limitations in our study. First, we must refer to the small sample size, especially in clinical evaluations. A larger number of samples would lead to more accurate results. Second, in clinical evaluation, we enrolled only patients with active RA. However, a previous study reported that plasma concentrations of TSP-1 are elevated in patients with RA, compared with healthy controls[11]. Therefore, we suspected that TSP-1 was particularly involved in the RA pathological condition.

Our study showed that TSP-1, strongly expressed in RA synovial tissues, is induced by TGF-β1. Further, the change of plasma TSP-1 by therapeutic intervention significantly correlated with the changes in disease activity. These findings indicate that TSP-1 might be critically involved in the disease process of RA, and considered as a useful biomarker not only for diagnostic purposes, but also for the evaluation of disease activity.

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International Journal of Rheumatic Diseases

International Journal of Rheumatic Diseases 2015; 18: 685–713

SPECIAL EDITORIAL REVIEW

APLAR rheumatoid arthritis treatment recommendations

Chak Sing LAU,[1] Faith CHIA,[2] Andrew HARRISON,[3] Tsu-Yi HSIEH,[4] Rahul JAIN,[5] Seung Min JUNG,[6] Mitsumasa KISHIMOTO,[7] Ashok KUMAR,[8] Khai Pang LEONG,[2] Zhanguo LI,[9] Juan Javier LICHAUCO,[10] Worawit LOUTHRENOO,[11] Shue-Fen LUO,[12] Peter NASH,[13] Chin Teck NG,[14] Sung-Hwan PARK,[6] Bagus Putu Putra SURYANA,[15] Parawee SUWANNALAI,[16] Linda Kurniaty WIJAYA,[17] Kazuhiko YAMAMOTO,[18] Yue YANG[9] and Swan Sim YEAP[19]

[1]*Division of Rheumatology and Clinical Immunology, Queen Mary Hospital, University of Hong Kong, Hong Kong,* [2]*Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore City, Singapore,* [3]*Department of Medicine, University of Otago Wellington, Wellington South, New Zealand,* [4]*Section of Allergy, Immunology and Rheumatology, and Section of Clinical Skills Training, Taichung Veterans General Hospital, Taichung, Taiwan,* [5]*Narayana Hospital, Jaipur, India,* [6]*Division of Rheumatology, Department of Internal Medicine, The Catholic University of Korea, St. Mary's Hospital, Seoul, South Korea,* [7]*Immuno-Rheumatology Center, St Luke's International Hospital, Tokyo, Japan,* [8]*Department of Rheumatology, Fortis Flt. Lt Rajan Dhall Hospital, New Delhi, India,* [9]*Department of Rheumatology, Peking University People's Hospital, Beijing, China,* [10]*St. Luke's Medical Center, Quezon City, Philippines,* [11]*Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand,* [12]*Department of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital and Chang Gung University, Tao-Yuan, Taiwan,* [13]*Department of Medicine, University of Queensland, Brisbane, Queensland, Australia,* [14]*Department of Rheumatology and Immunology, Singapore General Hospital, Singapore City, Singapore,* [15]*Rheumatology Division, Department of Internal Medicine, Brawijaya University, Saiful Anwar General Hospital, Malang, Indonesia,* [16]*Allergy, Immunology and Rheumatology Division, Internal Medicine Department, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand,* [17]*Division of Rheumatology, Department of Internal Medicine, University of Indonesia, Jakarta, Indonesia,* [18]*Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, and* [19]*Subang Jaya Medical Centre, Selangor, Malaysia*

Abstract

Aims: Rheumatoid arthritis is a chronic inflammatory condition that affects approximately 1% of the world's population. There are a wide number of guidelines and recommendations available to support the treatment of rheumatoid arthritis; however, the evidence used for these guidelines is predominantly based on studies in Caucasian subjects and may not be relevant for rheumatoid arthritis patients in the Asia-Pacific region. Therefore, the Asia Pacific League of Associations for Rheumatology established a Steering Committee in 2013 to address this issue.

Materials and methods: The AGREE II instrument and the ADAPTE Collaboration framework were applied to systematically identify, appraise, synthesize, and adapt international rheumatoid arthritis guidelines for use in the Asia-Pacific region.

Results: Forty rheumatoid arthritis treatment recommendations, based on evidence and expert opinion, were drafted and are presented in this report.

Correspondence: Professor Chak Sing Lau, Division of Rheumatology and Clinical Immunology, Queen Mary Hospital, University of Hong Kong, Hong Kong, Hong Kong.
Email: cslau@hku.hk

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Conclusion: The Asia Pacific of Associations for Rheumatology rheumatoid arthritis treatment recommendations are intended to serve as a reference for best practice management of rheumatoid arthritis in Asia-Pacific, focusing on local issues to ensure the delivery of basic care for these patients, and to improve their outcomes. In addition, the document will serve as a reference for national rheumatology associations in Asia-Pacific for developing guidelines in their respective countries.

Key words: drug treatment, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology that affects approximately 1% of the global population.[1–3] The disease is characterized by inflammation, pain, stiffness and progressive joint destruction leading to high rates of morbidity and mortality in the affected individuals.[1–3] Furthermore, RA is associated with productivity losses and increased financial burden, increased psychological distress, depression and, consequently, significantly decreased health-related quality of life.[4–6]

Disease-modifying antirheumatic drugs (DMARDs) form the cornerstone of RA treatment. These agents have the capacity to modify the disease process by reducing or reversing signs and symptoms, disability, impairment of quality of life, inability to work, and progression of joint damage.[7] Early and aggressive treatment with DMARDs has been shown to be effective in altering the clinical course of RA, and slowing or stopping the radiographic progression. DMARDs are broadly classified into conventional DMARDs (cDMARDs) including synthetic chemical agents such as methotrexate, sulfasalazine and leflunomide, and biological DMARDs (bDMARDs), including: tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab); the T-cell costimulation inhibitor, abatacept; the anti-B cell agent, rituximab; the interleukin (IL)-6 receptor (IL-6R)-blocking monoclonal antibody, tocilizumab; as well as the IL-1 inhibitor, anakinra. Recently, tofacitinib, a Janus kinase (JAK) inhibitor, has also been shown to have disease-modifying effects in RA.

NEED FOR RA RECOMMENDATIONS IN THE ASIA-PACIFIC (AP) REGION

As the evidence used in most international RA treatment guidelines is obtained predominantly from studies in Caucasian subjects, these guidelines may not be relevant for RA patients in the AP countries. Data show that there is an increased prevalence of certain infections (e.g., tuberculosis [TB], hepatitis B and C infection, Epstein–Barr virus infection)[8,9] and malignancies (e.g., T-cell and natural killer-cell lymphomas,[10] stomach cancer[11]) in the AP region. Thus, a Steering Committee under the auspice of the Asia Pacific League of Associations for Rheumatology (APLAR) was formed in 2013 to formulate AP region-specific treatment recommendations for RA that address AP-specific issues.

However, the AP region has vast intra-regional diversity in terms of ethnicities, socioeconomic structures and health resources; these characteristics also differ from those in Western countries. Furthermore, the availability and dosage of medications vary across AP countries. Thus, it is difficult to develop RA treatment recommendations that will be appropriate for all AP countries. Owing to a shortage of rheumatologists, RA patients in the region are also often managed by general practitioners and allied health practitioners. Consequently, the treatment practices are not standardized and vary widely, even within countries. Furthermore, there are limited data from the AP region to endorse evidence-based recommendations that may be considered more appropriate in some countries in the region. Nevertheless, this Steering Committee aimed to develop recommendations that will be as evidence-based as possible and define the best practices for managing RA in the AP region.

In addition, the Steering Committee also made recommendations based on expert opinion and consensus so that countries with limited resources may be able to achieve the minimum essential standard of care for their RA patients.

TARGET AUDIENCE AND CONTENTS

The intended target audience for this document includes rheumatologists and all practitioners who manage RA. It focuses predominantly on recommendations for the pharmacological treatment of RA. The document includes 40 recommendations across the following RA treatment domains: general RA treatment strategies; role of non-steroidal anti-inflammatory drugs (NSAIDs), including: cyclooxygenase-2 (COX-2) inhibitors; role of corticosteroids; role of conventional DMARDs