OPEN

Predictor of Hand Radiological Progression in Patients With Rheumatoid Arthritis Receiving TNF Antagonist Therapy by Change in Grayscale Synovitis—A Preliminary Study

Ying-Chou Chen, MD, Fu-Mei Su, MD,* Shih-Wei Hsu, MD,† Jia-Feng Chen, MD,* Tien-Tsai Cheng, MD,* Han-Ming Lai, MD,* and Wen-Chan Chiu, MD**

Objectives: This prospective study aimed to compare synovial ultrasound scores to conventional measures (DAS28, CRP levels) in predicting radiographic progression in patients with rheumatoid arthritis under TNF antagonist therapy.

Methods: Patients with RA who received TNF antagonist therapy were enrolled, all of whom underwent clinical, laboratory, and ultrasonographic assessments with grayscale and power Doppler assessments of bilateral elbows (anterior and posterior recess), wrists (dorsal, palmar, and ulnar aspects), second and third MCP joints (dorsal and palmar recess), and PIP II and III (dorsal and palmar) at baseline and at 1, 3 months. Hand radiographic damage was evaluated using van der Heijde modified Total Sharp Score (TSS) at baseline and 12 months.

Results: Thirty-two patients (384 joints, 832 synovial sites) continued the same treatment regimen for 12 months and completed the study, 41.6% of whom showed radiographic progression during the study period. Baseline DAS28 ($P = 0.123$), CRP level (P = 0.177), grayscale synovitis ($P = 0.092$), and power Doppler synovitis ($P = 0.120$) could not predict radiological damage in the TNF antagonist therapy group. However, ΔTSS was significantly related to changes in grayscale synovitis between baseline and 1 month ($P = 0.011$), but not at 3 months ($P = 0.591$), and was not related to changes in the power Doppler score at 1 ($P = 0.634$) and 3 months ($P = 0.298$).

Conclusions: Our data confirm that delayed improvement in grayscale synovitis between baseline and 1 month more accurately reflects 1-year radiological damage than conventional measures such as DAS28 score and CRP level. Therefore, we recommend serial ultrasound follow-up of patients with RA receiving TNF antagonist therapy.

Key Words: rheumatoid arthritis, grayscale synovitis, radiological progression, TNF antagonist

(*J Clin Rheumatol* 2017;23: 73–76)

From the Departments of *Rheumatology, and †Department of Radiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

The authors declare no conflict of interest.

Author contributions: Ying-Chou Chen designed and performed the research; Shih-Wei Hsu scored radiographs. Jia-Feng Chen performed ultrasound. Fu-Mei Su analyzed data, Tien-Tsai Cheng, Han-Ming Lai, Wen-Chan Chiu provided RA care. Ying-Chou Chen wrote the final paper.

This study was supported by Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung grant CMRPG8A0591.

Correspondence: Ying-Chou Chen, Department of Rheumatology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan. 123 Ta-Pei Rd, Niao-Sung District, Kaohsiung 833, Taiwan. E-mail: r820713@ms13.hinet.net.

Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000000516

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints. Immunologically mediated inflammation of the synovium causes cartilage destruction and bony erosion that can result in permanent disability.[1]

Before the development of targeted biological treatments, irreversible joint damage and deformity leading to a progressive decline in functional status and increased work disability were common outcomes for patients with RA. Biological treatments such as anti-TNFα have demonstrated an ability to inhibit radiographic progression in patients with either early or long-standing disease.[2,3]

Radiography, traditionally considered the "criterion standard" for assessing structural joint damage in patients with RA, is routinely used to diagnose and monitor RA patients and as an end point in clinical trials.[4]

Doppler ultrasound has been reported to be useful in predicting disease activity,[5] and cross-sectional studies have shown concurrent validity between Doppler and other validated measures of disease activity.[6–13] Furthermore, Doppler ultrasound has been used to assess patients with RA receiving anti–TNF-α treatment, showing the ability of Doppler ultrasound to aid in the monitoring of treatment.[14–17] The purpose of this study was to investigate the sensitivity to changes in overall grayscale and power Doppler ultrasound joint assessments and the predictive value of sequential parameters in the clinical and radiological outcomes of patients with RA who were receiving anti-TNF therapy.

METHODS

This prospective cohort study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Patients with RA aged 20 to 70 years who were approved by the Bureau of National Health Insurance for TNF-α therapy were included. Patients that had other systemic illnesses or infection were excluded.

All of the included patients underwent 28 swollen and 28 tender baseline clinical counts. Age, sex, ESR, and CRP level were recorded. The patients underwent radiography of the hands at baseline and after 1 year. The hand radiographs were collected and evaluated blindly in chronological order, using the criteria from Sharp score modified by van der Heijde et al.[18,19] For each patient, an erosion score, a joint-narrowing score, and a total radiographic score were recorded. The radiographs were scored in random order by an experienced observer (Shih-Wei Hsu) without knowledge of the clinical data. All patients underwent ultrasound assessments. The ultrasound scans were scored in random order by an experienced observer (Jia-Feng Chen) without knowledge of the clinical data.

Each patient underwent a musculoskeletal systematic multiplanar grayscale and power Doppler ultrasound examination using a MyLab 70 (Esaote, Firenze, Italy) system equipped with a multifrequency linear array transducer (6–18 MHz). The B-mode frequency ranged from 12 to 18 MHz for second and third MCP

TABLE 1. The Joints Presently Assessed and the Scans Used for the Semiquantitative Scoring (0–3) of B-Mode and Power Doppler Ultrasonography

Joints	Scanning and joint positioning
Elbow	Anterior recess
	Posterior recess
Wrist	Dorsal carpal recesses
	Ulnar aspects
	Volar carpal recesses
MCP 2	Dorsal recess
	Palmar recess
MCP 3	Dorsal recess
	Palmar recess
PIP 2	Dorsal recess
	Palmar recess
PIP 3	Dorsal recess
	Palmar recess

joint, and the power Doppler pulse repetition frequency was 750 Hz with a Doppler frequency of 6.7 to 11.1 MHz, and low wall filters were used. At the beginning of each scanning session at different sites, the focus was positioned at the level of the region of interest. Color gain was adjusted just below the degree that caused the appearance of noise artefacts. The color box was positioned at the level of the assessed site, and enlarged to the upper part of the image. The ultrasound assessments included elbow (anterior recess, posterior recess), wrist (dorsal, ulnar, and palm side), second MCP (dorsal side, palmar side), third MCP (dorsal side, palmar side), second PIP (dorsal side, palmar side), and third PIP joint (dorsal side, palmar side) (Table 1).

Grayscale synovitis was graded from 0 to 3 based on the system of Szkudlarek and colleagues,[11] with the equivocal "minimal" thickening graded as follows: grade 0, normal; grade 1, synovial thickening bulging over the line linking the tops of the periarticular bones; grade 2, grade 1 plus extension to 1 bone diaphysis; grade 3, grade 1 plus extension to both bone diaphyses. Synovitis in other joints was graded 0 to 3 as follows: 0, normal; 1, mild; 2, moderate; and 3, severe, in which grade 1 was defined as synovial thickening in excess of the mean plus 2 standard deviations of reference range when available. Synovial hyperemia was measured by power Doppler in each recess, and the maximal score was graded according to Szkudlarek et al: 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. Global ultrasound indices for grayscale synovitis and power Doppler were calculated by adding the scores from all joints. Ultrasound scans were performed before and at 1, 3 months after anti-TNF therapy.

The relationship between ultrasound activity and progression of radiological joint damage was then evaluated. The progression of 5 points during the 1 year of follow-up was defined as progression.

Intraobserver Reliability

Intraobserver reliability was evaluated before patients' inclusion by scoring for synovitis and PD signal in 20 recorded images of the joints included in the grayscale and PDUS assessment from 20 patients with active RA, by the investigator who coordinated the study (Jia-Feng Chen).

Statistical Analysis

Repeated measures analysis of variance was used to analyze the serial changes in ultrasound score. Multiple linear regression was used to adjust variables to predict radiological progression.

Intrarater reliabilities were evaluated using a 2-way mixed effects model using a consistency definition, in which the between-measure variance is excluded from the denominator variance, and both single measure and average measure intraclass correlation coefficients (ICCs) were calculated for total scores of both grayscale synovitis and PDUS. In addition, weighted κ values were calculated on a joint-by-joint level for both BM and PDUS scores. Intraclass correlation coefficient values and κ values are comparable; scores above 0.60 are considered good and scores above 0.80 are very good.

RESULTS

From December 2011 to December 2014, 32 patients were approved by the Bureau of National Health Insurance to receive biological therapy (24 adalimumab, 8 etanercept). The patients had a mean age of 56.9 years; all had severe RA, and most were female. The mean BMI was 21.6 ± 4.3 kg/m^2, and the mean DAS28 was 7.3 ± 0.3 wa (Table 2). The baseline grayscale synovitis score was 29.71 ± 8.13, and the power Doppler score was 17.79 ± 12.14. After anti-TNF therapy, the grayscale synovitis score decreased to 22.96 ± 9.12 at 1 month and 17.38 ± 4.33 at 3 months. The power Doppler score decreased to 3.92 ± 3.32 at 1 month and 3.50 ± 2.34 at 3 months (Table 3). While the hand radiography showed progression in 41.6% of patients.

Intraobserver Reliability and Sensitivity to Change of the PDUS Assessments

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

Intraobserver Reliability and Sensitivity to Change of the Radiographic Assessments

Intraobserver ICCs for the baseline radiographs were 0.83 (95% confidence interval [CI], 0.65–0.92) for the erosion score, 0.91 (95% CI, 0.79–0.95) for the JSN score, and 0.96 (95% CI, 0.89–0.99) for the total score. Intraclass correlation coefficients for the 12-month radiographs were 0.72 (95% CI, 0.28–0.91) for the erosion score, 0.87 (95% CI, 0.62–0.92) for the JSN score, and 0.90 (95% CI, 0.69–0.97) for the total score.

TABLE 2. Clinical and Laboratory Characteristics of the Patients at Baseline

	Mean	SD
Age, mean (SD), year	56.9	13.9
Female, n (%)	18 (75)	
Body height, cm	159.4	6.4
Body weight, kg	56.2	9.0
Body mass index, kg/m^2	21.6	4.3
DAS28	7.3	0.67
ESR, mm/h	56.9	26.2
CRP, mg/dL	27.6	28.4

© 2017 The Author(s). Published Wolters Kluwer Health, Inc.

TABLE 3. Serial Sonographic Composite Scores Before and After Anti-TNF Therapy

Variable	Mean	SD	Minimum	Maximum
Synovitis_0 month	29.71	8.13	13	39
Synovitis_1 month	22.96	9.12	9	37
Synovitis_3 month	17.38	4.33	11	27
Dop_0 month	17.79	12.14	0	38
Dop_1 month	3.92	3.32	0	11
Dop_3 month	3.50	2.34	0	9

We evaluated the factors contributing to radiographic progression and found that baseline age, sex, BMI, DAS28, ESR, and CRP levels could not predict radiological progression. In addition, ultrasound parameters showed that no improvements in grayscale synovitis after 1 month of anti-TNF therapy could predict radiological changes ($P = 0.011$), and that no change in grayscale at 3 months and the power Doppler score at 1 and 3 months could not predict future radiological progression (Table 4).

DISCUSSION

The accurate assessment of joint inflammation and sensitive monitoring of disease activity in patients with RA is essential when evaluating responses to treatment and disease outcome. In RA, synovitis appears to be the primary abnormality responsible for structural joint damage[20]; therefore, the monitoring of therapy of patients with RA should focus on synovitis. It is known that synovial inflammation consists of periarticular vasodilatation followed by synovial proliferation, which is accompanied by angiogenesis resulting in intra-articular blood vessel formation. Hypervascularization and angiogenesis of the synovial membrane are considered to be the primary pathogenic mechanisms responsible for the invasive behavior of rheumatoid pannus. Therefore, there is a relationship between joint inflammatory activity and synovial vascularization. Joint synovitis has traditionally been assessed indirectly by means of inflammatory subjective clinical data and laboratory parameters. However, imaging techniques such as musculoskeletal ultrasound are playing an increasingly important role in the evaluation and monitoring of patients with chronic inflammatory arthritis.

High-resolution ultrasound is being increasingly used in the analysis of RA. Grayscale ultrasound is used to visualize joint structures, enabling a distinction between synovial hypertrophy and other causes of apparent joint swelling such as subcutaneous edema and tenosynovitis. Power Doppler allows for the assessment of synovial vascularity and hence a distinction between inflamed and nonvascular synovial swelling. Nevertheless, few studies have reported on the predictive value of longitudinal ultrasound joint assessments on radiological progression in RA. In this study, a combination of grayscale (presence of joint effusion and/or synovial hypertrophy) and power Doppler findings (presence and grade of intra-articular power Doppler signals) in ultrasound was used.

Although changes in grayscale synovitis and power Doppler ultrasound parameters were parallel throughout the study, we find delay improvement in grayscale synovitis at 1 month to be a measurement of radiological progression independent of standard clinical and laboratory variables after 1 year of anti-TNF therapy.

Taylor et al[14] previously evaluated the prognostic value of ultrasound in RA in a randomized controlled trial of patients with early RA receiving anti-TNF therapy. They reported that the baseline synovial vascularization detected by power Doppler in MCP joints correlated with the radiographic joint damage over the following year.

However, severe RA is associated with high DAS28, ESR, and CRP levels, so when using anti-TNF to treat this group it is difficult to predict radiological progression using these markers alone. In fact, in our study, none of these parameters could predict radiological progression, and so we used ultrasound. Using ultrasound, we found that no improvements in grayscale synovitis at 1 month could be used to predict radiological progression, and that no improvements in the power Doppler synovitis score could not be used to predict damage in anti-TNF user. A possible reason for this may be that grayscale synovitis reflects pannus formation, so after 1 month of anti-TNF treatment the lack of improvements in synovitis may reveal severe pannus formation with a poor response to anti-TNF suppression, which would then lead to future radiological progression. Power Doppler synovitis only reflects the change in hyperemia, which may be dissociated from improvements of pannus formation. Consistent with this hypothesis, several studies have reported that anti-TNF therapy can halt radiological progression, despite no improvements in power Doppler activity.[21] If patients on anti-TNF therapy did not use longitudinal ultrasound assessment, we could not found the changes in synovial hypertrophy and loss the data of no improvement in synovial proliferation. So the prediction of future radiological progression will be only based on clinical assessment, but as in our data, DAS28, ESR, and CRP were poor predictors in these situations. If we used ultrasound as a serial follow-up tool, we can see more intra-articular changes, and gained more information on prediction future effect and radiological prognosis. Therefore, we suggest that it would be better to use the grayscale synovitis score

TABLE 4. Factors Influencing Radiological Progression

	Regression Coefficient	Standard Error	*t*	*P*
Age	*0.01*	*0.01*	*1.16*	*0.254*
Sex	*−0.42*	*0.23*	*−1.84*	*0.074*
BMI	*0.03*	*0.03*	*1.03*	*0.309*
DAS28	*0.13*	*0.35*	*0.36*	*0.719*
ESR	*−0.11*	*0.01*	*−1.35*	*0.184*
CRP	*0.00*	*0.00*	*−0.11*	*0.913*
No improvement of grayscale synovitis score between month 0 and month 1	0.50	0.22	2.25	0.036
No improvement of grayscale synovitis score between month 0 and month 3	0.04	0.70	0.05	0.487
No improvement of power Doppler score between month 0 and month 1	0.04	0.36	0.11	0.653
No improvement of power Doppler score between month 0 and month 3	0.29	0.36	0.80	0.250

© 2017 The Author(s). Published Wolters Kluwer Health, Inc.

to predict radiological changes in the patients receiving anti-TNF therapy.

There are several limitations to this study. First, the study was conducted in accordance with daily clinical practice, and the patients were treated with various disease modifying anti-rheumatic drugs (DMARDs), oral corticosteroids, and NSAIDs at variable doses during the study. Therapeutic decisions were made without knowledge of the ultrasound findings, and therefore we could not compare the predictive value of power Doppler ultrasound variables based on the DMARDs prescribed, evaluate the potential role of different DMARDs in power Doppler ultrasound parameters, or study the effect of power Doppler ultrasound findings when making therapeutic decisions. Moreover, the rheumatologist who performed the ultrasound scans could not be completely unaware of the joint signs and symptoms of the patients. To avoid as much bias as possible, the ultrasound examinations were carried out by an independent operator.

Despite the decreased power Doppler activity in ultrasound, there was persistent radiographic progression. We evaluated the factors and found that a poor improvement in grayscale synovitis at 1 month was associated with progression. Therefore, the detection of no improvements in grayscale synovitis in RA could be considered a strong predictor of disease aggressiveness in anti-TNF treatment, which is important when making treatment decisions.

Key Messages

Lack of improvement in grayscale synovitis between baseline and 1 month more accurately reflects 1-year radiological damage than conventional measures such as DAS28 score and CRP level in RA receiving TNF antagonist therapy.

REFERENCES

1. Menke J. Photoacoustic breast tomography prototypes with reported human applications. *Eur Radiol*. 2015;25:2205–2213.
2. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999; 340:253–259.
3. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med*. 2000;343:1586–1593.
4. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum*. 2002;46:328–346.
5. Brown AK, Quinn MA, Karim Z, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum*. 2006;54:3761–3773.
6. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Estimation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis. *Ann Rheum Dis*. 2003;62:1049–1053.
7. Naredo E, Gamero F, Bonilla G, et al. Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: comparison of extended versus reduced joint evaluation. *Clin Exp Rheumatol*. 2005;23:881–884.
8. Hameed B, Pilcher J, Heron C, et al. The relation between composite ultrasound measures and the DAS28 score, its components and acute phase markers in adult RA. *Rheumatology (Oxford)*. 2008;47:476–480.
9. Naredo E, Collado P, Cruz A, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. *Arthritis Rheum*. 2007;57:116–124.
10. Terslev L, Torp-Pedersen S, Savnik A, et al. Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. *Arthritis Rheum*. 2003;48: 2434–2441.
11. Szkudlarek M, Narvestad E, Klarlund M, et al. Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. *Arthritis Rheum*. 2004;50:2103–2112.
12. Walther M, Harms H, Krenn V, et al. Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum*. 2001; 44:331–338.
13. Ellegaard K, Torp-Pedersen S, Terslev L, et al. Ultrasound colour Doppler measurements in a single joint as measure of disease activity in patients with rheumatoid arthritis—assessment of concurrent validity. *Rheumatology (Oxford)*. 2009;48:254–257.
14. Taylor PC, Steuer A, Gruber J, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum*. 2004;50:1107–1116.
15. Iagnocco A, Perella C, Naredo E, et al. Etanercept in the treatment of rheumatoid arthritis: clinical follow-up over one year by ultrasonography. *Clin Rheumatol*. 2008;27:491–496.
16. Iagnocco A, Filippucci E, Perella C, et al. Clinical and ultrasonographic monitoring of response to adalimumab treatment in rheumatoid arthritis. *J Rheumatol*. 2008;35:35–40.
17. Naredo E, Moller I, Cruz A, et al. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis Rheum*. 2008; 58:2248–2256.
18. van der Heijde DM, van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet*. 1989;1:1036–1038.
19. van der Heijde D, Simon L, Smolen J, et al. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a roundtable discussion. *Arthritis Rheum*. 2002;47:215–218.
20. Conaghan PG, O'Connor P, McGonagle D, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. *Arthritis Rheum*. 2003;48:64–71.
21. Døhn UM, Ejbjerg B, Boonen A, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Ann Rheum Dis*. 2011;70:252–258.

© 2017 The Author(s). Published Wolters Kluwer Health, Inc.