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

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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), andPIP II and III (dorsal and palmar) at baseline and at 1, 3, and 12 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, ADSS 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

Original Article

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-TNFαs have demonstrated an ability to inhibit radiographic progression in patients with either early or longstanding 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.14,15 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
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 posi-
tioned 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 sys-
tem 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 peri-
articular bones; grade 2, grade 1 plus extension to 1 bone diaphy-
sis; 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 devi-
ations of reference range when available. Synovial hyperemia was
measured by power Doppler in each recess, and the maximal score
was graded according to the level of the assessed site, and enlarged
from 0 to 3 as follows: 0, absent; 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. Ultra-
sound scans were performed before and at 1, 3 months after anti-
TNF therapy.

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

Intraobserver Reliability

Intraobserver reliability was evaluated before patients’ inclu-
sion 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).

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/m² and the mean
DAS28 was 7.3 ± 0.3 wa (Table 2). The baseline grayscale syno-
vitis 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 synovitis and PDUS the median (range) per-
centages 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 0.87 (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 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        |
|                 | Volar carpal recesses         |
|                 | Ulnar aspects                 |
| MCP 2           | Dorsal recess                 |
|                 | Palmar recess                 |
| MCP 3           | Dorsal recess                 |
|                 | Palmar recess                 |
| PIP 2           | Dorsal recess                 |
|                 | Palmar recess                 |
| PIP 3           | Dorsal recess                 |
|                 | Palmar recess                 |

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/m² | 21.6 | 4.3 |
| DAS28             | 7.3    | 0.67|
| ESR, mm/h         | 56.9   | 26.2|
| CRP, mg/dL        | 27.6   | 28.4|

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 gray-
scale 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 compara-
ble; scores above 0.60 are considered good and scores above
0.80 are very good.
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\(^2\); therefore, the monitoring of therapy for RA, synovitis appears to be the primary abnormality responsible when evaluating responses to treatment and disease outcome. In monitoring of disease activity in patients with RA is essential. Radiological changes \( \text{in grayscale synovitis after 1 month of anti-TNF therapy could predict radiological changes} \) \( (P = 0.011) \), 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).

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\(^4\) 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.\(^2\) If patients on anti-TNF therapy did not use longitudinal ultrasound assessment, we could not find 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 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       |

### 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 |
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 pa-
tients 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 vari-
able based on the DMARDs prescribed, evaluate the potential
role of different DMARDs in power Doppler ultrasound parame-
ters, 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 un-
aware 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 synovi-
tis 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 aggressiv-
ness in anti-TNF treatment, which is important when making
treatment decisions.

Key Messages

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

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