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# Ultrasound is more reliable than inflammatory parameters to evaluate disease activity in patients with RA receiving tocilizumab therapy

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## ABSTRACT

The target of treatment for rheumatoid arthritis (RA) is to keep low disease activity or remission. Tocilizumab can fully inhibit interleukin-6 and C reactive protein (CRP) production. The goal of the study is to search whether tocilizumab treatment compared with adalimumab treatment had the similar effect on sonography and inflammatory parameters in patients with RA. We compared ultrasound scores and inflammatory parameters between patients with RA receiving tocilizumab therapy and those receiving adalimumab therapy. Power Doppler (PD) ultrasound and grayscale synovial hypertrophy on bilateral radiocarpal joints were performed. Inflammatory mediators and ultrasound scores were compared by independent t-test between the adalimumab and tocilizumab groups. 65 patients with RA (32 tocilizumab and 33 adalimumab) were included. Between the two groups, there were no significant differences in age, gender, rheumatoid factors and anticyclic citrullinated peptide antibody. Following biological therapy, the ultrasound score was 2.33 in the tocilizumab group and 2.08 in the adalimumab group (p=0.570), while the erythrocyte sedimentation rate, CRP and Disease Activity Score in 28 joints (DAS28) were lower in the tocilizumab group. So ultrasound scores between the two groups were not significantly different, but the laboratory parameters and DAS28 were lower in the tocilizumab group than in the adalimumab group. Hence, to assess disease activity cannot be based only on clinical evaluations, so we suggest PD ultrasound to be used for all patients on tocilizumab therapy and reflect the true disease activity in these patients.

### Significance of this study

**What is already known about this subject?**

- The previous gold standard of evaluation of rheumatoid arthritis (RA) treatment was to use clinical parameters such as the Disease Activity Score in 28 joints (DAS28) to evaluate disease activity.
- Among the biological agents, tocilizumab has been shown to fully inhibit the effect of interleukin-6 and C reactive protein (CRP) production, thereby leading to decreases in CRP and erythrocyte sedimentation rate.
- Musculoskeletal ultrasound has been used to assess the efficacy of drug treatment in RA.

**What are the new findings?**

- Clinical parameters improved after tocilizumab therapy, but there was still residual sonographic activity at the wrist joint.
- We also found that despite relatively lower clinical disease activity compared with adalimumab, the sonography score was similar between these two drugs.
- Therefore, only using DAS28 as a guide to therapy will lead to misinterpretation of disease status, when disease activity is still visible in imaging studies.

**How might these results change the focus of research or clinical practice?**

- Disease activity cannot be evaluated only on clinical evaluations. We recommend power Doppler ultrasound to be used for all patients on tocilizumab therapy and assess the disease activity in these patients.

## INTRODUCTION

The target of treatment for rheumatoid arthritis (RA) is to keep low disease activity or complete remission.[1–6] The previous gold standard of evaluation was to use clinical parameters such as the Disease Activity Score in 28 joints (DAS28) to evaluate disease activity. However, biological agents have significantly reduced disease activity by suppressing synovitis and reducing subsequent joint destruction.[7 8] Among the biological agents, tocilizumab has been shown to fully inhibit the effect of interleukin-6 (IL-6) and C reactive protein (CRP) production,[9] thereby leading to decreases in CRP and erythrocyte sedimentation rate (ESR). Musculoskeletal ultrasound has been used to evaluate the efficacy of drug treatment in RA. In this study, we were interested in investigating whether tocilizumab therapy had the similar efficacy as adalimumab



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based on imaging studies,[10] and whether this would influence the prediction of RA activity in daily practice.

## MATERIALS AND METHODS

RA was diagnosed based on the 1987 American College of Rheumatology criteria.[11] The indications for biological disease-modifying antirheumatic drugs (DMARDs) (adalimumab and tocilizumab) treatment were severe RA (DAS >5.1) in combination with two DMARDs for longer than 6 months. The exclusion criteria were age ≤20 years or >80 years, and those with other systemic illnesses or infections.

We compared patients with RA who were receiving tocilizumab and adalimumab treatment, and evaluated ultrasound scores and inflammatory parameters. Power Doppler (PD) ultrasound and grayscale (GS) synovial hypertrophy were on bilateral radiocarpal joints. Inflammatory mediators and ultrasound scores were compared by independent t-test.

GS and PD ultrasound examinations were assessed using a MyLab 70 system (Esaote, Firenze, Italy). The B-mode frequency was set at 12–18 MHz for the wrist, and the PD pulse repetition frequency was 750 Hz. The focus was positioned at the level of the region of interest.

GS synovitis was graded from 0 to 3 (where 0=absence, 1=mild, 2=moderate, and 3=marked). PD was graded from 0 to 3 (where 0=absence, no synovial flow; 1=mild, ≦3 isolated signals; 2=moderate, >3 isolated signals or confluent signal in less than half of the synovial area; and 3=marked, signals in more than half of the synovial area) during the ultrasound examination.[12] Ultrasonography was performed before and 6 months after adalimumab or tocilizumab therapy.

### Statistical analysis

The results were expressed as mean±SD or percentage. The $\chi^2$ test was used for categorical variables. Independent t-test was used to compare the score of the two groups. All statistical tests were two-sided and significance was set at $p<0.05$. All analyses were assessed using SPSS V.24.0 software.

### Intrarater reliability

Intrarater reliability was evaluated by a two-way mixed-effects model. Using a consistent definition between-measures variance was excluded from the denominator variance, and both single measure and average measure intraclass correlation coefficients (ICCs) were calculated for total scores of both GS and PD. Weighted κ values were also calculated on a joint-by-joint level for both GS and PD scores. The ICC and κ values were compared, with scores >0.60 considered as good and scores >0.80 as very good.

## RESULTS

Thirty-two patients received adalimumab and 33 received tocilizumab from December 2013 to December 2016. The patients had a mean age of 55.37±13.06 (adalimumab) and 54.63±14.72 (tocilizumab) years. Most of them were female, and all had severe RA (table 1). There were no differences between the two groups in smoking, alcohol consumption, body mass index, systemic diseases or the use of disease-modifying antirheumatic disease medications (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, and ciclosporin).

**Table 1** Baseline demographic and clinical characteristics of patients with rheumatoid arthritis who received biological therapy

| Variables | Adalimumab (n=32) | Tocilizumab (n=33) | p Value |
|---|---|---|---|
| Age (years) | 55.37±13.06 | 54.63±14.25 | 0.829 |
| Gender (female, %) | 27 (84.4) | 24 (72.7) | 0.367 |
| Body mass index (kg/m$^2$) | 22.58±3.86 | 23.06±4.18 | 0.631 |
| Baseline DAS28 score | 6.59±0.44 | 6.34±0.64 | 0.43 |
| Diabetes | 3 (9.4) | 6 (18.2) | 0.475 |
| Hypertension | 8 (25.0) | 15 (45.5) | 0.12 |
| Liver disease | 3 (9.4) | 6 (18.2) | 0.475 |
| Kidney disease | 0 (0) | 0 (0) | 0.317 |
| Heart disease | 3 (9.4) | 0 (0) | 0.114 |
| Pulmonary disease | 4 (12.5) | 3 (9.1) | 0.708 |
| Use of other RA medications | | | |
| Methotrexate | 23 (71.9) | 18 (54.5) | 0.2 |
| Hydroxychloroquine | 26 (81.3) | 18 (54.5) | 0.053 |
| Leflunomide | 9 (28.1) | 6 (18.2) | 0.389 |
| Ciclosporin | 3 (9.4) | 6 (18.2) | 0.475 |
| Sulfasalazine | 2 (6.3) | 0 (0) | 0.238 |
| Glucocorticoid use | 18 (56.3) | 24 (72.7) | 0.2 |

DAS28, Disease Activity Score in 28 joints; RA, rheumatoid arthritis.

After biological therapy for 6 months, the ESR was 34.2±14.51 mm/hour in the adalimumab group and 11.88±3.77 mm/hour in the tocilizumab group (p=0.001), and the CRP level was 6.39±4.37 mg/dL in the adalimumab group and 0.97±0.89 mg/dL in the tocilizumab group (p=0.001) (figure 1). The combined ultrasound score in the adalimumab group was 3.50±1.29, compared with 3.22±2.06 in the tocilizumab group (p=0.386) (table 2).

## DISCUSSION

Composite indices are used to evaluate RA disease activity. Based on the tenderness of swollen joints rated by visual analog scale by the physician and the patient, ESR, and/or CRP level, each patient is classified into remission,

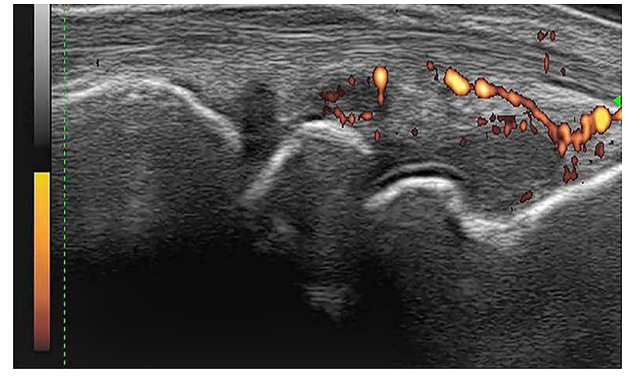

**Figure 1** A 60-year-old man receiving tocilizumab therapy. The grayscale score at the radiocarpal joint was grade 2, while the erythrocyte sedimentation rate was 28 mm/hour and the C reactive protein level was 2.5 mg/L.

**Table 2** Comparison between tocilizumab and adalimumab groups based on laboratory and ultrasound scores

| | Adalimumab (n=32) | Tocilizumab (n=33) | p Value |
|---|---|---|---|
| ESR (mm/hour) | 34.2±14.51 | 11.88±3.77 | 0.001 |
| CRP (mg/dL) | 6.39±4.37 | 0.97±0.89 | 0.001 |
| DAS28 | 4.92±0.57 | 4.14±0.67 | 0.013 |
| Ultrasound scores | 3.50±1.29 | 3.22±2.06 | 0.386 |

CRP, C reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate.

low, moderate, or high disease activity groups.[13 14] Ultrasonography is more precise than clinical and physical examinations in appraising synovitis,[15 16] and issues of ultrasound operator dependency are not significant when performed by trained sonographers following standardized joint scans.[17]

The trial reported that tocilizumab alone is superior to adalimumab alone in reducing RA activity in patients for whom methotrexate was ineffective.[18] The same results have also been reported in other studies related to tocilizumab and tumor necrosis factor inhibitors.[19 20]

In this study, we found that although clinical parameters improved after tocilizumab therapy, there was still residual sonographic activity at the wrist joint. We also found that despite relatively lower clinical disease activity compared with adalimumab, the sonography score was similar between these two drugs. Therefore, only using DAS28 as a guide to therapy will lead to misinterpretation of disease status, when disease activity is still visible in imaging studies.

The dissociation between clinical parameters and sonographic activity may be because tocilizumab is a more potent inhibitor of IL-6, so strongly decreasing acute phase reactants, leading to greater decreases in laboratory data and subsequently a relatively lower DAS28. However, synovial membrane hypertrophy and hyperemia do not decrease as quickly as laboratory parameters.

Tocilizumab interrupts the binding of IL-6 to its receptor, and had a direct effect on acute phase reactants such as CRP and ESR. Tocilizumab can adequately decrease symptoms in patients without treatment target with traditional treatment. The results of our analysis show that tocilizumab therapy is superior to adalimumab by DAS28 alone in patients with active RA. However, using ultrasound to achieve residual synovial activity is equivalent to adalimumab. Therefore, in patients using tocilizumab as biological therapy, clinicians cannot rely only on laboratory parameters, and the addition of ultrasound of the joint is needed to evaluate synovitis and improve clinical judgment. From this point of view, to use DAS28 as a treat-to-target regimen is not suitable at least in those with tocilizumab therapy. Further studies are needed to elucidate whether this can predict more sophisticated future radiographic progression.

There are several limitations to this study. This is an observational study and not randomized. Treatment is likely to be influenced by the characteristics of the patients with RA and other factors such as the preference of administration routes. Also, we had no comparison of tocilizumab with other biologics and Health Assessment Questionnaire (HAQ) data. Although some joints such as the shoulders and knees were not included in the ultrasound evaluations, they would have the same baseline DAS28, ultrasound activity and medical history, thereby lessening the impact of compounding factors. In addition, it lacked radiographic data. Due to the importance of joint protective effects in demonstrating clinical efficacy, evaluating sonographic changes in patients treated with these drugs will be necessary in the future.

## CONCLUSIONS

In conclusion, in the treatment of active RA, tocilizumab is a good choice for patients who cannot tolerate traditional treatment with the same efficacy to adalimumab therapy. In this study, the patients receiving tocilizumab therapy had lower laboratory parameters and clinical evaluations than those receiving adalimumab even though both groups had similar ultrasound scores. Hence, disease activity cannot be assessed only by clinical evaluations. We suggest that PD ultrasound can be used to evaluate all patients on tocilizumab therapy and reflect the disease activity in these patients.

**Contributors** W-CC designed and performed the research. J-FC performed the ultrasonography. C-HK, C-YH and H-ML analyzed the data. C-HK provided the rheumatoid arthritis care. Y-CC wrote the final paper. W-CC and H-ML had the same contribution.

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**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** This prospective cohort study was approved by CMRP Kaohsiung Chang Gung Memorial Hospital Institutional Review Board.

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## REFERENCES

1 Mok MY, Danda D. 'Treat to target' for rheumatoid arthritis in 2014--time tested triple therapy or logical biologics? *Int J Rheum Dis* 2014;17:1–3.
2 Harrold LR, Reed GW, Harrington JT, *et al*. The rheumatoid arthritis treat-to-target trial: a cluster randomized trial within the Corrona rheumatology network. *BMC Musculoskelet Disord* 2014;15:389.
3 Ten Klooster PM, Vonkeman HE, Oude Voshaar MA, *et al*. Predictors of satisfactory improvements in pain for patients with early rheumatoid arthritis in a treat-to-target study. *Rheumatology* 2015;54:1080–6.
4 Huizinga T, Knevel R. Rheumatoid arthritis: 2014 treat-to-target RA recommendations--strategy is key. *Nat Rev Rheumatol* 2015;11:509–11.
5 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
6 Farman S, Ahmad NM, Saeed MA, *et al*. Treat-to-target approach in daily clinical practice in Pakistani patients with early Rheumatoid Arthritis. *J Coll Physicians Surg Pak* 2015;25:129–33.
7 van der Heijde D, Klareskog L, Rodriguez-Valverde V, *et al*. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54:1063–74.

8 Tada M, Koike T, Okano T, *et al*. Comparison of joint destruction between standard- and low-dose etanercept in rheumatoid arthritis from the Prevention of Cartilage Destruction by Etanercept (PRECEPT) study. *Rheumatology* 2012;51:2164–9.
9 Suzuki T, Hirota T, Ogishima H, *et al*. Subclinical inflammation with tocilizumab treatment of rheumatoid arthritis: MRI evaluation for 2 years. *Int J Rheum Dis* 2015;18:108–10.
10 Dale J, Purves D, McConnachie A, *et al*. Tightening up? Impact of musculoskeletal ultrasound disease activity assessment on early rheumatoid arthritis patients treated using a treat to target strategy. *Arthritis Care Res* 2014;66:19–26.
11 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
12 Naredo E, Rodríguez M, Campos C, *et al*. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheum* 2008;59:515–22.
13 Anderson J, Caplan L, Yazdany J, *et al*. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res* 2012;64:640–7.
14 Gaujoux-Viala C, Mouterde G, Baillet A, *et al*. Evaluating disease activity in rheumatoid arthritis: which composite index is best? a systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI. *Joint Bone Spine* 2012;79:149–55.
15 Damjanov N, Radunovic G, Prodanovic S, *et al*. Construct validity and reliability of ultrasound disease activity score in assessing joint inflammation in RA: comparison with DAS-28. *Rheumatology* 2012;51:120–8.
16 Naredo E, Bonilla G, Gamero F, *et al*. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann Rheum Dis* 2005;64:375–81.
17 Backhaus M, Burmester GR, Gerber T, *et al*. Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001;60:641–9.
18 Gabay C, Emery P, van Vollenhoven R, *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381:1541–50.
19 Hyrich KL, Watson KD, Silman AJ, *et al*. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British society for rheumatology biologics register. *Rheumatology* 2006;45:1558–65.
20 Burmester GR, Feist E, Kellner H, *et al*. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). *Ann Rheum Dis* 2011;70:755–9.