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# Biological tapering and sonographic flare in rheumatoid arthritis

Chi-Hua Ko, Jia-Feng Chen, Tien-Tsai Cheng, Han-Ming Lai, Ying-Chou Chen

Department of Rheumatology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

## Correspondence to

Dr Ying-Chou Chen, Department of Rheumatology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung 833, Taiwan; r820713@ms13.hinet.net

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## ABSTRACT

This study aimed to evaluate the risk of ultrasound-detected synovitis after antitumor necrosis factor (TNF) tapering in patients with rheumatoid arthritis. We recruited patients with rheumatoid arthritis who accepted TNF tapering. Gray-scale synovitis and power Doppler score in bilateral wrists at the dorsal radiolunate joint were evaluated. We defined a sum of bilateral wrist scores of  $\geq 2$  as sonographic inflammation. Logistical regression analysis was used to adjust for confounding factors. One hundred and twenty-two patients who received a tapered dose of anti-TNF were enrolled, of whom 96 (78%) had ultrasound-detected synovitis and 26 had no inflammation. There were no significant differences in age, gender, body mass index, antinuclear antibodies, rheumatoid factor or anticitrullinated protein antibodies between the inflammation and non-inflammation groups. Moderate tapering of anti-TNF (tapering 50%) was more common in the patients with ultrasound-detected synovitis than mild tapering (tapering 25%) (68.8% vs 38.5%,  $p=0.005$ ). After adjusting for age, body mass index, gender and a 28-joint Disease Activity Score, the moderate tapering group still had a higher risk of ultrasound-detected synovitis (OR 5.786, 95% CI 1.986 to 16.852;  $p=0.001$ ); that is, the moderate tapering group had a 5.786 times higher risk of developing sonographic inflammation than the mild tapering group. The dose of biological tapering was the major determinant of ultrasound synovitis. Patients with moderate tapering had a higher risk of synovitis than those with mild tapering. We recommend not tapering by more than 25% to reduce subclinical inflammation and future joint damage.

## BACKGROUND

The use of biological agents to treat rheumatoid arthritis has improved clinical, structural, and functional outcomes.<sup>1</sup> However, ultrasound-detected residual synovitis can increase the risk of relapse and structural progression even in patients with clinical remission.<sup>2</sup> In fact, many patients considered to be in clinical remission according to the 28-joint Disease Activity Score (DAS28) still have residual synovitis on ultrasound.<sup>3</sup>

Recently, reducing the dose of biological agents or discontinuing therapy has been proposed.<sup>4–6</sup> However, there are currently no

## Significance of this study

### What is already known about this subject?

- ▶ Biological agents to treat rheumatoid arthritis have improved clinical, structural, and functional outcomes.
- ▶ Ultrasound-detected residual synovitis can increase the risk of relapse and structural progression in clinical remission. In fact, many patients considered to be in clinical remission according to the 28-joint Disease Activity Score (DAS28) still have residual synovitis on ultrasound.
- ▶ There are currently no data on ultrasound-detected synovitis in this era of biological tapering.

### What are the new findings?

- ▶ More patients in the sonographic inflammation group received anti-TNF tapering (moderate tapering, 50%) (68.8% vs 38.5%,  $p=0.005$ ).
- ▶ After adjusting for age, body mass index, gender and DAS28, the moderate tapering group still had a higher risk of sonographic inflammation (OR 5.786, 95% CI 1.986 to 16.852;  $p=0.001$ ).
- ▶ The patients with moderate tapering had a 5.786 times higher risk of developing sonographic inflammation than those with mild tapering.

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

- ▶ The dose of biological tapering was the major determinant of ultrasound synovitis. The patients with moderate tapering had a higher risk of synovitis than those with mild tapering.
- ▶ We recommend not tapering by more than 25% to reduce subclinical inflammation and future joint damage.

data on ultrasound-detected synovitis in this era of tapering biological agents. Previous studies have reported that power Doppler (PD) synovitis can be used to predict radiographic structural progression.<sup>7</sup> Therefore, in this study, we aimed to determine synovitis by ultrasound in patients receiving a tapered dose of antitumor necrosis factor (anti-TNF) and to assess the



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risk of developing ultrasound-detected synovitis in these patients.

## METHODS

This was an observational ultrasound study based on a semi-quantitative B-mode and Doppler score assessed by rheumatologists. We recruited all patients with rheumatoid arthritis who received tapering of anti-TNF from January 2012 to December 2015. The Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital approved this study. The inclusion criteria were: (1) using anti-TNF for more than 2 years and (2) those with low disease activity before anti-TNF tapering; that is, a DAS28 of  $\leq 3.2$ . We defined mild tapering as a dose reduction of 25% and moderate tapering as a dose reduction of 50% every 3 months. Patients with a serious infection were excluded.

Clinical and laboratory data and DAS28 before starting anti-TNF and before reducing anti-TNF were retrospectively reviewed. We evaluated the ultrasonographic findings after tapering for 1 year in both wrists at the dorsal radiolunate joint<sup>8</sup> using a MyLab 70 XVisionGold (Esaote, Firenze, Italy) system. To evaluate gray-scale synovitis (GS), the ultrasonographic scans were scored in random order by an experienced observer (Jia-Feng Chen) without knowledge of the clinical data. GS was graded from 0 to 3 based on the system used by Szkudlarek and colleagues.<sup>9</sup> Synovial hyperemia was measured in the joint recess on power Doppler imaging, and the maximal score was graded according to the grading system used by 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. We defined a bilateral wrist score (GS + PD) of  $\geq 2$  as sonographic inflammation.

## STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS V.22.0 (SPSS). Comparisons between independent means were analyzed using the independent t-test, and relationships between categorical variables were evaluated using the  $\chi^2$  test. Logistical regression analysis was used to adjust for potential confounding factors.

## RESULTS

Among the 122 enrolled patients (63 etanercept, 59 adalimumab), 96 (78%) had sonographic inflammation and 26 had no inflammation. There were no significant differences in age, gender, body mass index, antinuclear antibodies (ANA), rheumatoid factor (RF), or anticitrullinated protein antibodies (ACPA) between the inflammation and non-inflammation groups (table 1). The DAS28 before starting anti-TNF therapy was slightly higher in the non-inflammation group ( $p=0.035$ ); however, there was no significant difference in DAS28 before tapering anti-TNF therapy between the two groups. There were also no significant differences in disease modifying antirheumatic drugs between the two groups. More patients with moderate anti-TNF tapering (tapering 50%) had sonographic inflammation than those with mild tapering (tapering 25%) (68.8% vs 38.5%,  $p=0.005$ ) (figure 1).

After adjusting for age, body mass index, gender, and DAS28, the moderate tapering group still had a higher risk of sonographic inflammation (OR 5.786, 95% CI 1.986 to 16.852;  $p=0.001$ ) (table 2), and those with moderate tapering had a 5.786 times higher risk of developing sonographic inflammation than those with mild tapering. Positive ANA was a confounding factor for the risk of sonographic inflammation (OR 3.806, 95% CI 1.176 to 12.319;  $p=0.026$ ).

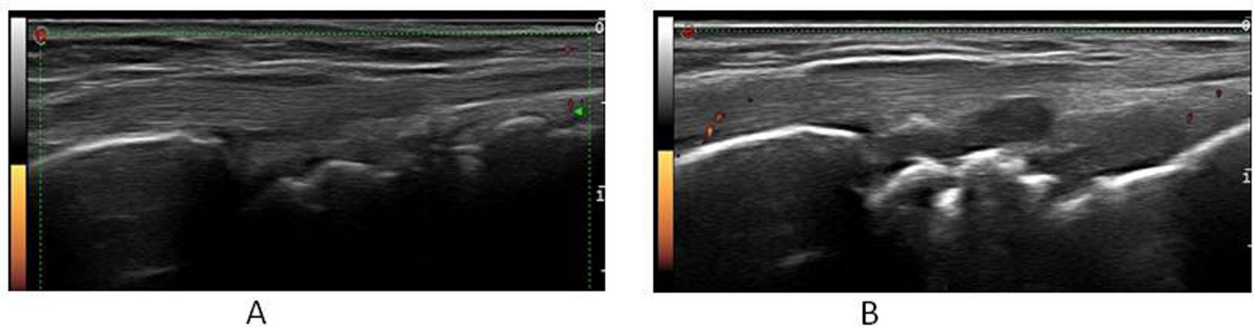
## DISCUSSION

Our results showed that the patients who received a tapered dose of biological agents had a higher rate (78%) of sonographic inflammation. Synovitis is an important factor in managing patients with rheumatoid arthritis in clinical remission.<sup>10–16</sup> Previous studies have used the DAS28 to assess reductions in the dose of biological agents, and this has been shown to increase the risk of future disease flares or radiographic progression. The validity of synovitis to predict subsequent structural deterioration irrespective of the joint examination modality has also been studied.<sup>17</sup> The wrist is the predominant site of inflammation examined in MRI studies (53%),<sup>18</sup> so in this study we used a bilateral wrist score (GS+PD) of  $\geq 2$  as subclinical inflammation.<sup>19</sup>

**Table 1** Baseline demographic and clinical characteristics of the patients with and without subclinical inflammation

	Sonographic inflammation (n=96)	No sonographic inflammation (n=26)	p-Value
Age, years (SD)	59.06 $\pm$ 10.79	57.53 $\pm$ 8.83	0.509
Gender (female, %)	76 (79.2)	22 (84.6%)	0.378
Body mass index (kg/m <sup>2</sup> )	22.54 $\pm$ 3.31	23.73 $\pm$ 4.76	0.144
ANA (n, %)	34 (35.4)	6 (23.1%)	0.346
RF (n, %)	80 (83.3)	21 (80.8%)	0.479
ACPA (n, %)	79 (82.6)	22 (83.1%)	0.577
DAS28 score before starting anti-TNF therapy	6.62 $\pm$ 0.47	6.84 $\pm$ 0.40	0.035
DAS28 score before tapering anti-TNF therapy	2.51 $\pm$ 0.36	2.55 $\pm$ 0.34	0.645
Methotrexate (n, %)	70 (72.9)	26 (27.1%)	0.445
Hydroxychloroquine (n, %)	84 (87.5)	21 (80.8%)	0.357
Sulphasalazine (n, %)	17 (17.7)	2 (7.7%)	0.174
Leflunomide (n, %)	2 (2.1)	2 (7.4%)	0.199
Ciclosporin (n, %)	2 (2.1)	0 (0%)	0.618
Anti-TNF tapering (moderate tapering, %)	66 (68.8)	10 (38.5%)	0.005

ACPA, anticitrullinated protein antibodies; ANA, antinuclear antibody; RF, rheumatoid factor; DAS28, 28-joint Disease Activity Score; TNF, tumor necrosis factor.



**Figure 1** The mild tapering group (A) had grade 1 synovitis, while the moderate tapering group (B) had grade 2 synovitis.

**Table 2** Multivariate analysis of the ORs for sonographic inflammation

	Regression coefficient	SE	Wald	p Value	OR	95% CI for OR	
						Lower	Upper
Anti-TNF tapering (moderate tapering/mild tapering)	1.755	0.545	10.357	0.001	5.786	1.986	16.852
ANA	1.337	0.599	4.975	0.026	3.806	1.176	12.319
RF	0.188	0.710	0.070	0.791	1.207	0.300	4.858
ACPA	0.412	0.527	0.614	0.433	1.511	0.538	4.240
Age	0.045	0.027	2.867	0.090	1.046	0.993	1.103
Gender	0.181	0.738	0.060	0.806	1.198	0.282	5.090
Body mass index (kg/m <sup>2</sup> )	-0.133	0.068	3.855	0.050	0.876	0.767	1.000
DAS28 score before starting anti-TNF	-1.089	0.607	3.223	0.073	0.336	0.102	1.105
DAS28 score before tapering anti-TNF therapy	0.126	0.799	0.025	0.874	1.135	0.237	5.434

ACPA, anticitrullinated protein antibodies; ANA, antinuclear antibody; DAS28, 28-joint Disease Activity Score; RF, rheumatoid factor; TNF, tumor necrosis factor.

In this study, the major determinant of ultrasound synovitis was dose of biological agent. Those with a 50% reduction in anti-TNF dose (moderate tapering) had a higher risk of ultrasound synovitis than those with mild tapering. Therefore, we suggest that moderate reduction should not be used as an option for biological tapering.

GS and PD scores have been shown to identify residual synovial inflammation before discontinuation of treatment.<sup>20</sup> Doppler synovitis has also been shown to have value in predicting failure in dose tapering.<sup>21</sup> Taken together, these findings validate that synovitis can predict subsequent structural deterioration irrespective of the joint examination modality.<sup>17</sup> Ultrasound-detected synovitis may be related to incomplete suppression of inflammation, and a negative finding of synovitis can provide greater confidence of remission and greater certainty of good long-term outcomes, whereas a positive finding of synovitis suggests a greater likelihood of disease flares and subsequent adverse long-term clinical, functional, and quality of life outcomes.<sup>22</sup>

This study has several limitations. First, only 122 patients underwent ultrasonographic assessments, and this small number limited the statistical modeling. However, these patients are representative of those in general rheumatology clinics. Second, we chose ultrasonography to assess bilateral wrist joint regions within a feasible period, as this is a pragmatic and practical approach in a busy clinical setting. Third, this is a cross-sectional ultrasound study, and it cannot fully explain the relationship between biological tapering and ultrasound inflammation.

In conclusion, the dose of biological tapering was the major determinant of ultrasound synovitis in this study. The patients with moderate tapering had a higher risk of synovitis than those with mild tapering. Therefore, we recommend not tapering the dose by more than 25% to reduce subclinical inflammation and future joint damage.

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**Contributors** CHK designed and performed the research. JFC performed the ultrasound. TTC and HML provided rheumatoid arthritis care. YCC wrote the final paper.

**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** This study was approved by the Ethics Committee of Kaohsiung Chang Gung Memorial Hospital and was carried out in accordance with the Helsinki Declaration. Ethics approval and consent to participate: this retrospective study was approved by the Institutional Review Board of our hospital and informed consent was waived because of the retrospective nature of this study.

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