Deep clinical remission: an optimised target in the management of rheumatoid arthritis? Experience from an ultrasonography study

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Abstract

Objective

Treat-to-target strategy, aiming at clinical remission, has greatly improved the prognosis of RA. However, ultrasonographic subclinical synovitis is correlated with bone erosion and disease flare. The aim of this study was to evaluate whether deeper clinical remission (DAS28(ESR)≤1.98) reflects the better control of subclinical synovitis.

Methods

One hundred and twenty-six RA patients in clinical remission were enrolled in the study. Disease activity and ultrasongraphy were evaluated at baseline, and every 3 months during a 12-month follow-up. The power Doppler (PD) synovitis and synovial hypertrophy (SH) of 22 joints were recorded semi-quantitatively. The relationship between the extent of clinical remission, flare and ultrasonographic features was analysed.

Results

In 126 RA patients, 76 achieved deep clinical remission (defined as DAS28(ESR)≤1.98) and 50 achieved mild clinical remission (defined as 1.98<DAS28(ESR)≤2.6). At baseline, PD synovitis and SH were detectable in 25 (32.9%) and 34 (44.7%) in 76 patients in deep clinical remission, which were significantly less compare with those in the mild group (32.9% vs. 72.0% and 44.7% vs. 78.0%, p<0.01 for both). In all, 54 (42.9%) patients relapsed at average of 6.8±3.3 months during follow-up. Patients in deep remission possessed not only lower risk to relapse (30.3% vs. 62.0%, p<0.01), but also longer duration of remission before relapse (8.1±3.3 vs. 5.9±3.1 months, p<0.05). Besides, applying DAS28(ESR)<1.895 to predict ultrasonographic remission defined as negativity of both PD and SH was highly accurate (p<0.001). Subclinical PD synovitis at baseline was an independent risk factor for predicting relapse in RA patients achieved clinical remission (OR 8.8 [95% CI 2.7-28.4]).

Conclusion

Subclinical synovitis was common in RA patients even in deep clinical remission. The deeper the clinical remission, the milder the subclinical synovitis, and the lower risk to relapse. Therefore, achieving deeper clinical remission, which reflected better control of subclinical synovitis and less tendency to flare, could be an optimised treatment target of RA.

Key words

rheumatoid arthritis, deep clinical remission, subclinical synovitis, ultrasonographic remission, relapse

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Introduction

Rheumatoid arthritis (RA) is an articular inflammatory disease with inevitable bone destruction or even joint deformity if not treated early and properly. In the recently years, treat-to-target strategy, aiming at clinical remission or low disease activity, has already greatly improved the outcomes of RA (1). And systematic monitoring of real-life RA patients with a treat-to-target strategy with real-time feedback to the physician was proved feasible in routine care (2). However, some studies showed that, in those RA patients who had already achieved and even maintained clinical remission for 2 years, 31% to 52% of them relapsed (3) and 19% to 30% had a radiological progression during follow-up (4), which indicates that clinical remission is not an optimised target in terms of long-term management of RA. Meanwhile, the concept of deep clinical remission, defined as DAS28(ESR) ≤1.98 was introduced in a recent clinical trial (5). The data showed that up to 79% of RA patients in deep clinical remission avoided a relapse after discontinuation of adalimumab for one year, which was comparable to the group who continued adalimumab. Hence, it is speculated that achieving deep clinical remission, a stricter state of remission, may reduce the risk of relapse and prevent imaging progression.

Musculoskeletal ultrasonography (MSUS) as a novel imaging technique has remarkable advantages, for instance, being non-radioactive, non-invasive, easily-accepted, and sensitive in detecting synovitis with good reproducibility (6). Our previous study showed that, subclinical synovitis detected by power Doppler ultrasonography was observed in 33%–52% of RA patients who achieved clinical remission defined by whatever criteria, including DAS28(CRP), DAS28(ESR), CDAI, SDAI and 2010 ACR/EULAR criteria (7). We proceeded with a prospective study in RA patients in clinical remission, to evaluate whether deeper clinical remission could reflect the better control of ultrasonographic subclinical synovitis and imply less relapse.

Patients and methods

Patient recruitment

One hundred and twenty-six RA patients in clinical remission from rheumatology clinic of Peking University First Hospital between March 2012 and June 2014 were enrolled in this study. All the patients fulfilled the 2010 ACR/EULAR classification criteria for the diagnosis of RA. Clinical remission was defined when DAS28(ESR) was ≤2.6 at two consecutive visits 3 months apart. RA treatment needed to be stable for at least 3 months, and no clinical indication for a change in treatment. Relapse was defined as a DAS28(ESR) >2.6 following a period of clinical remission. The research protocol was approved by Peking University First Hospital Institutional Review Board for clinical research and all participants signed informed consent form before entering the study in compliance with the Helsinki Declaration.

Clinical assessment

All the 126 patients were prospectively followed up for 12 months. Clinical and laboratory examinations, disease activity assessments and ultrasonography were performed every 3 months for each patient. The following variables were collected: age, gender, disease duration, swollen joint counts (SJC) and tender joint counts (TJC). The following laboratory results were recorded: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). RF was measured by rate nephelometry (ULN≤20IU/ml) and anti-CCP was detected by ELISA (ULN≤5RU/ml). Disease activity indexes including DAS28(ESR), DAS28(CRP), CDAI and SDAI were calculated for each patient at each follow-up visit. Deep remission and mild remission were respectively defined as DAS28(ESR) ≤1.98 and 1.98<DAS28(ESR) ≤2.6 (5).

Ultrasonography was performed by 2 well-experienced rheumatologists who were blinded to all clinical findings. 22 joints (bilateral wrists, metacarpophalangeal joints (MCP1-5) and proximal interphalangeal joints (PIP1-5) were scanned from dorsal aspect on transverse and longitudinal planes.

Table I. Baseline demographics, clinical and ultrasonographic characteristics of the 126 RA patients in clinical remission.

Female, n (%)	92 (73.0%)
Age (years)	48.4 ± 15.3
Disease duration (years)	5.2 ± 6.1
TJC	0.3 ± 0.6
SJC	0.3 ± 0.7
ESR (mm/h)	11.5 ± 7.1
CRP (mg/L)	3.8 ± 3.0
PGA	13.4 ± 9.4
EGA	10.8 ± 6.5
DAS28 (ESR)	1.89 ± 0.50
DAS28 (CRP)	1.41 ± 0.38
CDAI	2.8 ± 1.9
SDAI	3.2 ± 2.2
Fulfilling 2010 ACR/EULAR criteria, n (%)	69 (54.8%)
Positive RF, n (%)	93 (73.8%)
Positive anti-CCP, n (%)	98 (77.8%)
Ultrasonographic characteristics	
PD>0, n (%)	61 (48.4%)
SH>0, n (%)	73 (57.9%)
PD total score	2.0 ± 3.5
SH total score	2.6 ± 3.6
ultrasonographic remission (PD=0 and SH=0)	53(42.1%)
Tenosynovitis, n (%)	25 (19.8%)
Bone erosion, n (%)	55 (43.7%)

The measurement data were presented as mean±SD.

MCP2 and MCP5 joints were additionally assessed from the lateral aspect. Each scan took at least 15 minutes. The Esoate Mylab 90 machine with a 6-18 MHz transducer was used in our study

Power Doppler (PD) subclinical synovitis and grey-scale synovial hypertrophy (SH) were measured and graded using the 2001 Sukudlarek semi-quantitative method on a scale of 0–3 (8) (PD: 0=absence or minimal flow; 1=mild: single vessel signal; 2=moderate: confluent vessels signals in <50% of the joint area; 3=marked: confluent vessel signals in >50% of the joint area. SH: 0= no synovial thickening; 1=mild: synovial thickening without bulging over the line linking tops of the periarticular bones; 2=moderate: synovial thickening bulging over the line linking tops of the periarticular bones; 3=severe: synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses).

PD total score was defined as the sum of PD scores at each joint (0–66). Similarly, SH total score was defined as the sum of SH scores at each joint (0-66). Ultrasonographic remission was referred to the state of both PD total score and SH total score of 0. PD>0 stands for the patient who has joints with ultrasonographic PD synovitis, SH>0 stands for the patient who has joints with ultrasonographic grey-scale synovial hypertrophy. PD joint counts means total joint counts with PD>0, SH joint counts means total joint counts with SH>0.

Besides, the presence of tenosynovitis and bone erosion in bilateral hands (dorsal aspect of MCP1-5 and PIP1-5) and dorsal aspect of bilateral wrists in our RA patients was also evaluated at each visit. The tenosynovitis and bone erosion were defined according to pathological changes in articular inflammatory diseases in Outcome Measurement In Rheumatoid Arthritis and Connective Tissue (OMERACT).

Statistical analysis

For quantitative data which was presented as mean±SD, *t*-test was used for the comparisons between two groups, while non-parametric test (Mann-Whitney U-test) was used for non-normally distributed variables. Chi-square test was applied for qualitative data. Spearman correlation analysis was used in identifying the linear correlation. The area under ROC curve was evaluated for diagnostic value. Logistic regression analysis was performed to predict risk factors. All statistical analyses were done with SPSS v. 17.0 software. *p*-values <0.05 were considered significant.

Results

Demographic and clinical features

The demographics, baseline clinical and ultrasonographic characteristics of the enrolled patients were shown in Table I. 92 (73.0%) of 126 patients were female. The mean age was 48.4±15.3 with 5.2±6.1 years as the mean disease duration. At baseline, power Doppler synovitis (PD>0) was detected in 61 (48.4%) patients and grey-scale synovial hypertrophy (SH>0) was detected in 73 (57.9%) patients. Ultrasonographic remission (PD=0 and SH=0) was only observed in 53 (42.1%) patients.

Comparisons of the baseline clinical and ultrasonographic features between RA patients who achieved deep and mild remission

According to the different degree of remission, 126 patients were further divided into two groups, deep remission group (76 patients) and mild remission group (50 patients). In the deep remission group, 25 (32.9%) patients showed PD synovitis (PD>0) and 34 (44.7%) patients showed grey-scale synovial hypertrophy (SH>0). Compared with the mild remission group, patients in deep remission had lower ESR and CRP (p=0.000 and p=0.003), lower PD and SH total score, fewer PD and SH joint counts (p<0.01). Besides, fewer patients in deep remission had ultrasonographic PD synovitis and SH compare with the mild group (32.9% *vs*. 72.0%) (p<0.01) (44.7% *vs*. 78.0%) (p<0.01) which means more patients from deep remission group reached ultrasonographic remission than those from mild remission group (55.3% *vs*. 22.0%) (P<0.01) (Table II).

Compared to patients in mild clinical remission, patients in deep remission have lower risk to relapse (30.3% *vs*. 62.0%) (p<0.01) and longer duration before relapse (8.1±3.3 *vs*. 5.9±3.1 months) (p<0.05) during the 12 months follow up (Table II).

Correlations between the disease activity scores and ultrasonographic features in patients who achieved clinical remission

Further analysis between the disease activity score and ultrasonographic

Table II. Comparisons of the baseline clinical and ultrasonographic features and ratio of relapse between RA patients in deep remission and in mild remission.

	Patients in deep remission (n=76)	Patients in mild remission (n=50)	*p*
Female, n (%)	54 (71.1%)	38 (76.0%)	>0.05
Age (years)	47.2 ± 15.6	50.2 ± 14.8	>0.05
Disease duration (years)	4.7 ± 5.6	6.1 ± 6.8	>0.05
TJC	0.2 ± 0.5	0.4 ± 0.7	>0.05
SJC	0.2 ± 0.7	0.4 ± 0.6	>0.05
ESR (mm/h)	8.2 ± 3.8	16.5 ± 8.0	**0.000**
CRP (mg/L)	3.1 ± 2.4	4.9 ± 3.6	**0.003**
PGA	11.6 ± 8.0	16.1 ± 10.7	**0.013**
EGA	9.5 ± 5.6	12.8 ± 7.4	**0.008**
DAS28 (ESR)	1.58 ± 0.38	2.37 ± 0.18	**0.000**
DAS28 (CRP)	1.32 ± 0.32	1.56 ± 0.41	**0.001**
CDAI	2.3 ± 1.7	3.7 ± 2.0	**0.000**
SDAI	2.7 ± 2.1	4.1 ± 2.0	**0.000**
Fulfilling 2010ACR/EULAR criteria, n (%)	51 (67.1%)	18 (36.0%)	**0.001**
Positive RF, n (%)	54 (71.1%)	39 (78.0%)	>0.05
Positive anti-CCP, n (%)	58 (76.3%)	40 (80.0%)	>0.05
Ultrasonographic features			
PD>0, n (%)	25 (32.9%)	36 (72.0%)	**0.000**
SH>0, n (%)	34 (44.7%)	39 (78.0%)	**0.000**
PD total score	1.5 ± 3.7	2.6 ± 2.9	**0.049**
PD joint counts	0.7 ± 1.5	1.6 ± 1.5	**0.003**
SH total score	2.1 ± 3.8	3.4 ± 3.1	**0.047**
SH joint counts	1.2 ± 2.0	2.1 ± 2.0	**0.009**
ultrasonographic remission	42 (55.3%)	11 (22.0%)	**0.000**
Tenosynovitis, n (%)	14 (18.4%)	11 (22.0%)	>0.05
Bone erosion, n (%)	27 (35.5%)	28 (56.0%)	**0.023**
Relapse, n (%)	23 (30.3%)	31 (62.0%)	**0.001**
Duration before relapse(months)	8.1 ± 3.3	5.9 ± 3.1	**0.013**

The measurement data were presented as mean ± SD.

Table III. Correlations between the disease activity score and ultrasonographic PD or SH score in patients who achieved clinical remission.

	DAS28 (ESR)	
	r	*p*
PD total score	0.372	**<0.01**
PD joint counts	0.408	**<0.01**
SH total score	0.313	**<0.01**
SH joint counts	0.330	**<0.01**

The variables were non-normally distributed.

features in patients who achieved clinical remission by Spearman correlation analysis showed positive correlations between the disease activity score and the PD total score, SH total score and the PD and SH joint counts ($p<0.01$) (Table III).

These data indicated that a considerable proportion of RA patients in clinical remission, even in deep clinical remission, could not reach the ultrasonographic remission. Moreover, there were remarkably positive correlations between the disease activity score and the PD/SH total score, the PD/SH joint counts in RA patients who achieved clinical remission (Table III). Hence, we presumed that we could predict the ultrasonographic remission by using the disease activity score, for example DAS28(ESR), at a cut-off point.

When DAS28(ESR) was used to evaluate ultrasonographic remission, area under ROC curve (AUC) was 0.729 (Fig. 1), which was significantly different from 0.5 ($p<0.001$). The best cut-off for DAS28(ESR) was 1.895, which was highly accurate if DAS28(ESR)<1.895 was used to predict ultrasonographic remission.

Comparisons of baseline clinical and ultrasonographic characteristics between RA patients according to relapse or no relapse

Relapse occurred in 54 (42.9%) of 126 patients in clinical remission at baseline during 12 months of follow-up. The mean duration of relapse was 6.8±3.3 months. By comparing the baseline clinical and ultrasonographic features between the patients relapsed and not relapsed (Table IV), we noticed that in the relapsed group higher proportion of patients with ultrasonographic PD synovitis and SH, higher PD and SH total score and more PD and SH joint counts. On the contrary, more patients achieved ultrasonographic remission (PD=0 and SH=0) in the non-relapsed group ($p<0.01$). The DAS28(ESR) and proportion of patients who did not achieve 2010 ACR/EULAR criteria of remission was higher in the relapsed group. Importantly, no correlation was found between relapse and disease duration, baseline status of auto-antibodies, ultrasonographic tenosynovitis or bone erosion. Although the ESR was higher in the relapsed group, the value of ESR was within normal limits.

Independent risk factor for predicting the disease relapse

In RA patients achieved clinical remission, baseline DAS28(ESR), subclinical synovitis (PD>0), PD and SH total score were the possible risk factors to predict disease relapse (single factor analysis, data not shown here). But the baseline subclinical synovitis (PD>0) was the only independent factor to predict the relapse in RA patients who achieved clinical remission by logistic regression analysis (Table V).

Discussion

During recent years, rheumatologists have realised that the treat-to-target strategy, aiming at clinical remission, is often insufficient to stop bone erosion and prevent flare. Consist with the other studies in RA, our previous study showed that PD subclinical synovitis detected by ultrasonograpy

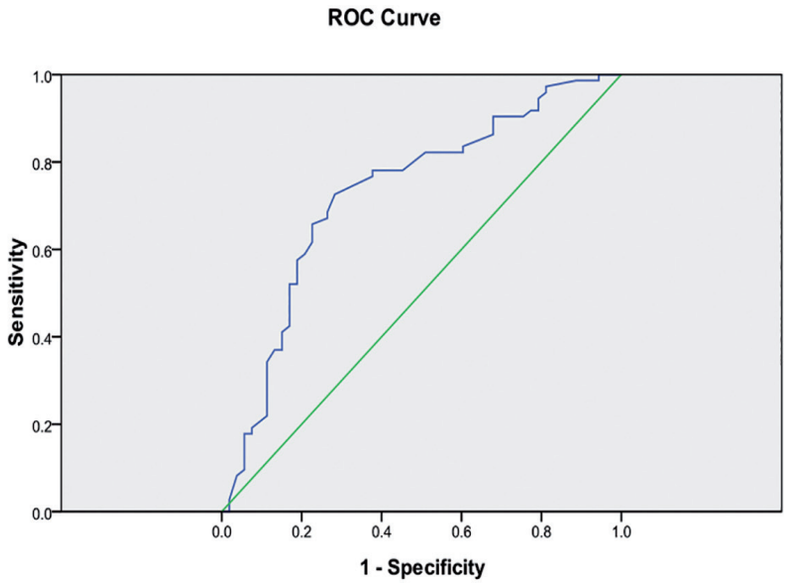

Fig. 1. ROC curve for DAS28(ESR) and ultrasonographic remission.

Table IV. Baseline clinical and ultrasonographic characteristics of the RA patients, according to relapse or no relapse.

	Relapse (n=54)	No relapse (n=72)	*p*
Female, n (%)	43 (79.6%)	49 (68.1%)	>0.05
Age (years)	47.5 ± 15.2	49.1 ± 15.4	>0.05
Disease duration (years)	5.4 ± 5.9	5.1 ± 6.4	>0.05
TJC	0.3 ± 0.6	0.3 ± 0.6	>0.05
SJC	0.4 ± 0.8	0.2 ± 0.6	>0.05
ESR (mm/hr)	13.7 ± 7.5	9.8 ± 6.4	**0.002**
CRP (mg/L)	4.2 ± 3.4	3.5 ± 2.7	>0.05
DAS28(ESR)	2.03 ± 0.47	1.79 ± 0.50	**0.007**
DAS28(CRP)	1.46 ± 0.36	1.38 ± 0.38	>0.05
CDAI	3.2 ± 2.0	2.6 ± 1.8	>0.05
SDAI	3.5 ± 2.0	3.0 ± 2.2	>0.05
2010ACR/EULAR criteria, n (%)	24 (44.4%)	45 (62.5%)	**0.044**
Positive RF, n (%)	36 (66.7%)	57 (79.2%)	>0.05
Positive anti-CCP, n (%)	39 (72.2%)	59 (81.9%)	>0.05
Ultrasonographic characteristics			
PD>0, n (%)	41 (75.9%)	20 (27.8%)	**0.000**
PD total score	3.1 ± 3.9	1.1 ± 2.8	**0.002**
PD joint counts	1.7 ± 1.7	0.6 ± 1.3	**0.000**
SH>0, n (%)	42 (77.8%)	31 (43.1%)	**0.000**
SH total score	3.6 ± 3.9	1.8 ± 3.1	**0.005**
SH joint counts	2.2 ± 2.2	1.0 ± 1.8	**0.001**
Ultrasonographic remission	12 (22.1%)	41 (56.9%)	**0.000**
Tenosynovitis, n (%)	15 (27.8%)	10 (13.9%)	>0.05
Bone erosion, n (%)	27 (50.0%)	28 (38.9%)	>0.05

The measurement data were presented as mean±SD.

commonly exists in 33.3~51.8% of the patients who achieved clinical remission defined by different clinical remission criteria (7). One research of JIA (juvenile idiopathic arthritis) also indicated the similar result that 38.2% JIA patients with clinical inactivity had evidence of synovial abnormalities in MSUS examination (9). The ultrasonographic subclinical synovitis has been confirmed to correlate with the progression of bone erosion and disease flare in RA patients achieved clinical remission (10, 11). In this study, the risk of relapse during the 12 months follow-up period was up to 42.9% in the patients who achieved clinical remission. The baseline subclinical synovitis (PD>0) was the only independent factor to predict the RA relapse.

So far there have been several studies suggesting that the PD subclinical synovitis could predict relapse of RA (12-14). A meta-analysis covering five relevant studies showed that subclinical synovitis, defined as double positivity of both the power Doppler and grey scale, was the independent factor to predict the relapse of RA patients after achieving clinical remission (OR 3.2 [95% CI 1.8–5.9]) (15). Our findings were consistent with these previous reports, indicating that good control of subclinical synovitis was the way to reduce the RA relapse.

How to better control the subclinical synovitis? There were some hints from our previous study showing that the stricter clinical remission criteria may reflect less subclinical synovitis (7). Recently, a concept of deep clinical remission was first introduced in a published clinical trial (5), in which flare, as a primary endpoint, was observed after discontinuation of adalimumab in RA patients who achieved clinical remission. They found that the patients in deep clinical remission had lower risk of relapse compared to those in mild remission. With the aim of trying to answer whether deep clinical remission reflects the better control of ultrasonographic subclinical synovitis, we set out to investigate the difference of ultrasonographic subclinical synovitis between RA patients in deep clinical remission and in mild clinical remission.

Our data demonstrated that both PD synovitis and grey-scale synovial hypertrophy were less detectable in RA patients in deep clinical remission than those in mild clinical remission, although the presence of subclinical synovitis remained very common in patients even after achieved deep clinical remission. Milder subclinical PD synovitis and SH were also observed in patients in deep clinical remission compared to patients in mild remission. Furthermore, in RA patients achieved clinical remission, there were apparent positive correlations between the clinical disease activity score and the PD total score, SH total score, joint counts with positive PD or SH. Furthermore, during the

Table V. Correlation between baseline parameters and relapse in RA patients who achieved clinical remission (Logistic regression analysis).

Baseline parameters	Relapsed group (n=54)	Non-relapsed group (n=72)	OR (95% CI)	*p*
PD>0, n (%)	41 (75.9%)	20 (27.8%)	**8.8 (2.7, 28.4)**	**0.000**
DAS28(ESR)	2.03 ± 0.47	1.79 ± 0.50	2.8 (1.0, 2.0)	0.058
PD total score	3.1 ± 3.9	1.1 ± 2.8	1.4 (0.9, 2.0)	0.100
SH total score	3.6 ± 3.9	1.8 ± 3.1	0.7 (0.5, 1.0)	0.071

The measurement data were presented as mean±SD.

12 months of follow-up, the patients in deep clinical remission showed a lower risk of relapse compared to patients in mild clinical remission. Therefore, our study indicated that achieving deeper degree of clinical remission means the better control of ultrasonographic subclinical synovitis and less tendency to flare. Deep clinical remission is probably an optimised treatment target in the management of RA.

We also found that applying DAS28(ESR)<1.895 may help clinicians to predict ultrasonographic remission in RA patients who achieved clinical remission. Another study conducted by Nemoto *et al*. claimed that the combination of SDAI/ CDAI remission, STAGE I/II and SJC12 <1 can act as strong predictors of the absence of PD signals in RA (16). Both of the studies indicated that routine clinical measures, especially disease activity score, could predict ultrasonography-determined synovitis and remission.

Treat-to-target has been and will be an important strategy in the treatment of RA. But how to define what we mean by remission should be very careful. The incremental benefit of pursuing imaging remission rather than clinical remission or deep clinical remission rather than the general clinical remission remains to be tested. In this study, we, for the first time, proposed that deep clinical remission could be an optimised treatment target by investigating the ultrasonographic subclinical synovitis and flare of RA patients during 1 year follow-up. There were some limitations of our study, for instance, the limited number of patients recruited. In the future, progression of bone erosion will be also included as an endpoint of the study in order to decide the different outcomes between the patients with different treating targets.

Conclusions

PD subclinical synovitis has been confirmed as a biological marker to predict the relapse of RA after achieving clinical remission. Subclinical synovitis presents in a considerable proportion of RA patients in clinical remission, even in deep clinical remission. Nevertheless, the deeper the clinical remission reflects milder ultrasonographic synovitis and lower risk to relapse which suggesting a better control of subclinical synovitis and flare. Hence, deeper clinical remission could be a better target in the management of RA.

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