A combination model to predict relapse and successful conventional DMARDs de-escalation in rheumatoid arthritis patients with sustained clinical remission

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Abstract

Objective

To determine the long-term outcomes of RA patients in sustained clinical remission under different therapeutic strategies and explore the risk factors to relapse.

Methods

RA patients in sustained clinical remission (DAS28(CRP) ≤2.6 for at least 6 months) were enrolled. Their baseline clinical features, ultrasonography and x-ray of hands were collected. The usage of conventional synthetic disease-modified anti-rheumatic drugs (csDMARDs) at baseline and every follow-up visits were recorded. Patients were divided into maintain-therapy group or de-escalate-therapy group according to their treatment during follow-up. The time-point of follow-up visits reaching 2 years or flare (DAS28(CRP)>2.6) was defined as the endpoint of the study. The risk factors to predict flare was analysed by logistic regression model.

Results

94 patients were enrolled in the study, with 59 in de-escalate-therapy group and 35 in maintain-therapy group. During an average of 20.8 months of follow-up, 40 (42.6%) patients relapsed, with 31 (52.5%) from de-escalate-therapy group and 9 (25.7%) from maintain-therapy group. De-escalate-therapy increased the risk of flare by 2.3 times (OR=3.38, p=0.044). Baseline DAS28(CRP) (OR=6.97, p=0.038), presence of subclinical synovitis (OR=3.67, p=0.024), combination of 2 csDMARDs (OR=3.72, p=0.030) were the risk factors for relapse, and the best cut-off value of DAS28(CRP) for relapse prediction through ROC curve was 1.82. Taking the three parameters into the model for a combined prediction probability, the area under the ROC curve was 0.722 (95% CI 0.61, 0.82, p=0.000).

Conclusion

De-escalation therapy was associated with higher risk of relapse in RA patients with sustained clinical remission. A combination model of DAS28(CRP)<1.82 and no subclinical synovitis may help to predict successful csDMARDs reduction in RA patients with sustained clinical remission receiving csDMARDs monotherapy.

Key words

rheumatoid arthritis, sustained clinical remission, treatment strategy, subclinical synovitis, relapse

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by joint inflammation, and subsequently irreversible bone erosion and joint deformity if improperly treated. Since the institution of treat-to-target (T2T) strategy aiming at clinical remission as well as the availability of biological agents in recent years, the prognosis of RA patients has been greatly improved (1, 2). The clinical remission rate of RA patients has been reported as high as 49%, and many patients can reach sustained clinical remission. But whether the treatment should be maintained or de-escalated, and how to de-escalate the therapy for those patients who have reached clinical remission or even sustained clinical remission are the new challenges for the rheumatologists.

Sustained remission is definitely important for better long-term outcome; however, relapse is common, especially in those RA patients receiving de-escalation therapy. It has been reported that approximately half of RA patients in clinical remission relapsed within 2 years (3-5). In the RETRO study, a prospective randomised controlled trial, 33.7% of the RA patients in sustained remission relapsed within 12 months, and importantly de-escalation, or discontinuation of DMARD therapy was associated with increased risk of relapse compared to maintain treatment strategy (6). On the other hand, some studies also showed that dose reduction was feasible in early RA patients treated with methotrexate and biologics while maintaining remission (7-9). A meta-analysis reported that a down-titration strategy was as effective as a continuation strategy for RA patients who achieved and maintained low disease activity or remission (10). Furthermore, several biomarkers including DAS28, anti-citrullinated protein antibodies (ACPA) positivity and presence of power Doppler under ultrasonography, were also reported to be associated with disease relapse (4, 11).

Due to economic reasons, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are most commonly used to maintain remission in Chinese RA patients. Whether reduction of csDMARDs is feasible in these patients after they have reached sustained remission remains unknown. Therefore, we set out to investigate the long-term outcomes of our RA patients in sustained clinical remission, under various treatment strategies, and further explore the risk factors associated with poor outcomes.

Methods

Patient recruitment

RA patients from rheumatology clinic of Peking University First Hospital between February 2013 and July 2015 were enrolled in this study. The inclusion criteria were:

1. fulfilled the 2010 ACR/EULAR classification criteria for RA;
2. reached sustained clinical remission defined as DAS28(CRP)≤2.6 for at least 6 months;
3. received ultrasound scan of the 22 joints of both hands at enrolment;
4. received csDMARDs therapy only.

Patient assessments

All the enrolled patients were prospectively followed up every 3 months under the principle of treat-to-target strategy. Two years of follow-up from baseline or flare was taken as the end point of the study. The therapeutic drugs were collected at baseline and all the follow-up visits. All the patients received the csDMARDs, including methotrexate, leflunomide, hydroxychloroquine, sulfasalazine. The use of glucocorticoids was also recorded. The therapy strategies adopted in these patients during follow-up were assorted into maintain-therapy or de-escalate-therapy based on the following principles. If de-escalation strategy was considered in a patient in sustained remission, glucocorticoid was the first to be de-escalated, then sulfasalazine and hydroxychloroquine, and Leflunomide or methotrexate was continuously used to the last. A patient with a decrease of dose and/or number of csDMARDs/glucocorticoid for at least 6 months during the whole periods of follow-up, was allocated into the de-escalate-therapy group, otherwise into the maintain group. For all the patients, the therapy strategy was decided by experienced

rheumatologists. When DAS28(CRP) was increased to over 2.6, the patient would be identified as disease relapse.

Clinical data collection

The following clinical data of the patients were collected: age, gender, disease duration, duration of reaching sustained clinical remission (defined as the periods from disease onset to reaching sustained clinical remission), the level of rheumatoid factor (RF) and ACPA at the diagnosis of RA. The data that were collected at baseline included: swollen joint counts (SJC) and tender joint counts (TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patient's global assessment (PGA), evaluator's global assessment (EGA) and ultrasonography including power Doppler synovitis, grey-scale synovial hypertrophy, the presence of tenosynovitis, bone erosion and osteophytes.

Ultrasonography was performed by 2 experienced rheumatologists who were blinded to all clinical data. The inter-observer reliability of the US evaluation between the operators was tested and analysed by intra-class correlation coefficient (ICC). The inter-observer reliability for grey-scale was 0.986 (95% CI 0.981–0.990) and 0.988 (95% CI 0.983–0.991) for power Doppler. 22 joints (bilateral wrists, metacarpophalangeal joints (MCP1-5) and proximal interphalangeal joints (PIP1-5)) were scanned from dorsal aspect on transverse and longitudinal planes. MCP2 and MCP5 joints were additionally assessed from the lateral aspect. The Esoate Mylab 90 machine with a 6–18 MHz transducer was used in our study.

The pathological changes on ultrasound were defined according to Outcome Measurement in Rheumatoid Arthritis and Connective Tissue (OMERACT). The synovitis was 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 (0–66) and SH total score (0-66) were defined as the sum of PD scores and SH scores at each joint, respectively. The subclinical synovitis was defined as total PD>0, and/or GS≥2.

Radiographic assessment

The x-rays of the wrist and hands at baseline and at the end of follow-up were assessed by using the van der Heidji modified Sharp score (mTSS). The mTSS was calculated as the joint space narrowing score (total 36 joints, 0–144) plus the erosion score (total 34 areas, 0–170). The ΔmTSS was defined as the average change of the mTSS per year. These assessments were performed by two experienced rheumatologists who were blind to the clinical features of the patients. The average ΔmTSS of the two evaluators was adopted for subsequent analysis.

Statistical analysis

The data were presented as means and SDs as well as medians and IQRs. Comparisons between the two groups were calculated using *t*-test for homogeneous parameters, non-parametric test (Mann Whitney U-test) for non-homogeneous parameters, and Chi-square test for categorical parameters. Logistic regression analysis was used to predict risk factors for disease relapse. The ROC curve based on logistic regression analysis was performed for the combine prediction probability. All statistical analysis was done with SPSS software v. 19.0. A *p*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the patients between the maintain-therapy group and de-escalate-therapy group

The demographics, baseline clinical features and ultrasonographic characteristics of the 94 enrolled patients were summarised in Table I. The mean age was 53.3±14.3 years with female predominance (67 patients, 71.3%). Their median disease duration was 33.5 (27.7, 44.3) months. The median duration of reaching sustained clinical remission was 11.2 (6.1, 21.5) months. The baseline DAS28(ESR) and DAS28(CRP) were 1.70±0.58 and 1.64±0.32, respectively. Ultrasonographic subclinical synovitis was detected in 30 (31.9%) patients. Mono, 2 and 3 DMARDs combination therapy were observed in 28 (29.8%), 52 (55.3%) and 14 (14.9%) patients respectively. Glucocorticoid was concomitantly used in 21 (22.3%) patients.

Among the 94 patients, 35 were in maintain-therapy group and 59 in de-escalate-therapy group. There was no obvious difference in duration of reaching sustained clinical remission, DAS28-ESR, DAS28-CRP, and ultrasonographic characteristics including the subclinical synovitis between the two groups at baseline. However, the drug usage of the two groups were significantly different. Most patients in maintain-therapy group received csDMARDs monotherapy (17 patients, 48.6%) or 2 csDMARDs combination therapy (14 patients, 40.0%), while 38 (64.4%) patients in de-escalate-therapy group received 2 csDMARDs combination therapy at baseline. The most commonly used csDMARDs in the 94 patients was methotrexate, followed by leflunomide, hydroxychloroquine and sulfasalazine, with no difference between the two groups. In addition, there were 19 (32.2%) patients in de-escalate-therapy group using glucocorticoid, which was statistically higher than the 2 (5.7%) patients in maintain-therapy group.

Comparisons of long-term outcomes between the maintain-therapy group and de-escalate-therapy group

During the first-year follow-up, 9 (15.3%) patients in the de-escalate-therapy group relapsed, which was similar to 4 (11.4%) patients in the maintain group. But during the second-year follow-up, the relapse was more often happened in the de-escalate-therapy group compared to the maintain-therapy group (31 patients, 52.5% *vs*. 9 patients, 25.7%, *p*=0.017).

Table I. Baseline characteristics of the patients between the maintain-therapy group and de-escalate-therapy group.

Characteristics	Total (n=94)	Maintain-therapy group (n=35)	De-escalate-therapy group (n=59)	*p*-value
Age, years	53.3 ± 14.2	55.5 ± 14.4	52.1 ± 14.2	0.266
Female, n (%)	67 (71.3%)	23 (65.7%)	44 (74.6%)	0.480
Disease duration, months	33.5 (27.7,44.3)	35.2 (28.9,44.3)	32.6 (27.1,44.2)	0.317
Duration of reaching SCR, months	11.2 (6.1,21.5)	13.2 (6.2,23.9)	8.8 (5.1,21.3)	0.453
Tender joint counts 28, n	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.467
Swollen joint counts 28, n	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.110
ESR, mm/1hr	10.7 ± 7.6	9.5 ± 6.0	11.4 ± 8.4	0.225
CRP, mg/dl	2.8 ± 2.3	2.6 ± 1.5	3.0 ± 2.6	0.381
DAS28(ESR)	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	0.565
DAS28(CRP)	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	0.888
RF positive, n (%)	77 (81.9%)	30 (85.7%)	47 (79.7%)	0.461
ACPA positive, n (%)	80 (85.1%)	30 (85.7%)	50 (84.7%)	0.899
Ultrasonographic characteristics				
PD score	0.0 (0.0, 1.0)	0.0 (0.0,1.0)	0.0 (0.0,1.0)	0.501
GS score	0.0 (0.0, 1.0)	0.0 (0.0,1.0)	0.0 (0.0,1.0)	0.571
Subclinical synovitis, n (%)	30 (31.9%)	12 (34.3%)	18 (30.5%)	0.820
Tenosynovitis, n (%)	12 (12.8%)	4 (11.4%)	8 (13.6%)	0.765
Bone erosion, n (%)	35 (37.2%)	14 (40.0%)	21 (35.6%)	0.669
Osteophytes, n (%)	43 (45.7%)	17 (48.6%)	26 (44.1%)	0.672
csDMARDs numbers used at baseline		0.009		
Single csDMARD, n (%)	28 (29.8%)	17 (48.6%)	11 (18.6%)	-
2 csDMARDs combination, n (%)	52 (55.3%)	14 (40.0%)	38 (64.4%)	-
3 csDMARDs combination, n (%)	14 (14.9%)	4 (11.4%)	10 (16.9%)	-
csDMARDs used at baseline				
Methotrexate	72 (76.6%)	25 (71.4%)	47 (79.7%)	0.451
Leflunomide	49 (52.1%)	19 (54.3%)	30 (50.8%)	0.832
Hydroxychloroquine,	41 (43.6%)	12 (34.3%)	29 (49.2%)	0.199
Sulfasalazine	5 (5.3%)	1 (2.9%)	4 (6.8%)	0.648
Glucocorticoid usage, n (%)	21 (22.3%)	2 (5.7%)	19 (32.2%)	0.003

SCR: sustained clinical remission; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28(ESR): disease activity score based on 28 joints and ESR; DAS28(CRP): disease activity score based on 28 joints and CRP; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; PD: power Doppler; GS: grey-scale; DMARDs: disease-modifying anti-rheumatic drugs.
The measurement data were presented as mean ± SD for normally distributed parameters and median (quartile range) for non-normally distributed parameters.

Table II. Comparison of relapse and radiographic progression between the maintain-therapy group and de-escalate-therapy group during two-year follow-up.

Outcomes	Maintain-therapy group (n=35)	De-escalate-therapy group (n=59)	*p*-value
Relapse during 1-year follow-up	4 (11.4%)	9 (15.3%)	0.761
Relapse during 2-year follow-up	9 (25.7%)	31 (52.5%)	0.017
ΔmTSS	0.6 ± 2.6*	0.8 ± 2.7^	0.168

ΔmTSS, the average change of modified Sharp score (mTSS) per year.
*Radiographic data were available for assessment in 27 patients;
^Radiographic data were available for assessment in 49 patients.

Among the 94 patients, radiographic data both at enrolment and the end of 2 year follow-up were available for assessment in 76 patients (27 patients in maintain-therapy group and 49 patients in de-escalate-therapy group). ΔmTSS between the two groups (0.6±2.6 *vs*. 0.8±2.7, *p*=0.168) was not significantly different, suggesting the similar radiographic progression (Table II).

Comparisons of the baseline features between patients who relapsed and those who did not

During the 2-year follow-up, relapse occurred to 40 (42.6%) of the 94 patients. The patients relapsed showed a tendency of shorter disease duration (31.2 *vs*. 34.6 months) and shorter duration of reaching sustained clinical remission (8.4 *vs*. 13.3 months). The clinical disease activity parameters at baseline, including ESR (12.8±7.9 *vs*. 9.2±7.1 mm/h, *p*=0.021), CRP (3.5±3.0 *vs*. 2.3±1.3 mg/ml, *p*=0.013), DAS28(ESR) (1.8±0.6 *vs*. 1.6±0.6, *p*=0.056) and DAS28(CRP) (1.7±0.4 *vs*. 1.6±0.2 *p*=0.018), were statistically higher in relapsed patients. We also observed the higher tendency of the ACPA positivity (92.5% *vs*. 79.6%) and presence of subclinical synovitis under ultrasound (42.5% *vs*. 24.1%) in the relapsed group (Table III). Relapse was statistically more often observed in patients with de-escalate-therapy strategy, which was consistent with the results in Table II. Although there was no statistical difference in the number of csDMARDs as well as glucocorticoid used between the two groups, we observed that 26 (65.0%) patients who relapsed were received combination of 2 csDMARDs at baseline.

Risk factors for predicting disease relapse

The risk factors to predict the disease relapse during long-term follow-up in RA patients who reached sustained clinical remission was explored by using logistic regression analysis. DAS28(CRP) (OR=4.99, *p*=0.025), de-escalate-therapy (OR=3.20, *p*=0.013) and two csDMARDs combination therapy (OR=2.92, *p*=0.015) were identified as risk factors for the subsequent relapse by univariate logistic regression analysis (Table IV). Although being statistically insignificant, duration of reaching sustained clinical remission, DAS28(ESR) and ACPA positivity, presence of subclinical synovitis, bone erosion and osteophytes on ultrasound, showed tendency to predict relapse. After bringing all the above parameters into the multivariate logistic regression model, we finally identified that DAS28(CRP) (OR=6.97, *p*=0.038), presence of subclinical synovitis (OR=3.67, *p*=0.024), de-escalate-therapy (OR=3.38, *p*=0.044) and 2 csDMARDs combination therapy (OR=3.72, *p*=0.030) at baseline were risk factors, and furthermore, the DAS28(CRP) and de-escalate-therapy were independent factors to predict relapse. On the other hand, duration of

Table III. Baseline characteristics of patients who relapsed and who did not relapse.

Parameters	Relapsed (n=40)	Not-relapsed (n=54)	*p*-value
Age, years	55.9 ± 13.8	51.4 ± 14.5	0.136
Female, n (%)	31 (77.5%)	36 (66.7%)	0.251
Disease duration, months	31.2 (27.2, 38.6)	34.6 (28.1, 50.1)	0.086
Duration of reaching SCR, months	8.4 (4.9, 17.4)	13.3 (6.2, 29.7)	0.076
Tender joint counts 28, n	0 (0,0)	0 (0,0)	0.233
Swollen joint counts 28, n	0 (0,0)	0 (0,0)	0.464
ESR, mm/1hr	12.8 ± 7.9	9.2 ± 7.1	0.021
CRP, mg/dl	3.5 ± 3.0	2.3 ± 1.3	0.013
DAS28(ESR)	1.8 ± 0.6	1.6 ± 0.6	0.056
DAS28(CRP)	1.7 ± 0.4	1.6 ± 0.2	0.018
RF positive, n (%)	35 (87.5%)	42 (77.8%)	0.226
ACPA positive, n (%)	37 (92.5%)	43 (79.6%)	0.083
Ultrasonographic characteristics			
Subclinical synovitis, n (%)	17 (42.5%)	13 (24.1%)	0.058
Tenosynovitis, n (%)	4 (10.0%)	8 (14.8%)	0.548
Bone erosion, n (%)	11 (27.5%)	24 (44.4%)	0.093
Osteophytes, n (%)	23 (57.5%)	20 (37.0%)	0.049
Numbers of csDMARDs used at baseline			0.081
1 csDMARD, n (%)	7 (17.5%)	21 (38.9%)	-
2 csDMARDs, n (%)	26 (65.0%)	26 (48.1%)	-
3 csDMARDs, n (%)	7 (17.5%)	7 (13.0%)	-
Glucocorticoid usage, n (%)	11 (27.5%)	10 (18.5%)	0.301
De-escalate-therapy patients,n (%)	31 (77.5%)	28 (51.9%)	0.011

SCR: sustained clinical remission; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28(ESR): disease activity score based on 28 joints and ESR; DAS28(CRP): disease activity score based on 28 joints and CRP; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; PD: power Doppler; GS: grey-scale; DMARDs: disease-modifying anti-rheumatic drugs.
The measurement data were presented as mean ± SD for normally distributed parameters and median (quartile range) for non-normally distributed parameters.

Table IV. The risk factors for predicting RA relapse by univariate logistic regression analysis.

Parameters	OR 95% CI)	*p*-value
Age	1.02 (0.99, 1.05)	0.137
Female gender	1.72 (0.67, 4.38)	0.254
Disease duration	0.97 (0.93, 1.00)	0.060
Duration of reaching SCR	0.97 (0.93, 1.00)	0.050
DAS28(ESR)	2.07 (0.97, 4.43)	0.059
DAS28(CRP)	4.99 (1.23, 20.39)	0.025
RF positivity	2.00 (0.64, 6.23)	0.232
ACPA positivity	3.16 (0.82, 12.17)	0.095
Presence of subclinical synovitis	2.33 (0.96, 5.65)	0.061
Presence of tenosynovitis	0.64 (0.18, 2.29)	0.492
Presence of bone erosion	0.47 (0.19, 1.14)	0.096
Presence of osteophytes	2.30 (0.99, 5.30)	0.051
De-escalate-therapy	3.20 (1.28, 7.98)	0.013
2 csDMARDs combination	2.92 (1.23, 6.92)	0.015
Glucocorticoid usage	1.67 (0.63, 4.43)	0.304

SCR: sustained clinical remission; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28(ESR): disease activity score based on 28 joints and ESR; DAS28(CRP): disease activity score based on 28 joints and CRP; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; DMARDs: disease-modifying anti-rheumatic drugs.

reaching sustained clinical remission (OR=0.95, p=0.015) seemed to be a protective factor (Table V).

ROC curve based on logistic regression analysis

Finally, we tried to propose a combined reference to help with successful reduction of csDMARDs therapy. DAS28(CRP) was first used to predict relapse through ROC curve, and the best cut-off for DAS28(CRP) was 1.82 although the area under the ROC curve was 0.610 (95% CI 0.49, 0.73) (p=0.069) (Fig. 1A). Then DAS28(CRP)>1.82, subclinical synovitis and 2 csDMARDs combination were included in the logistic regression analysis for a combined prediction probability. The area under the ROC curve was 0.722 (95% CI 0.61, 0.82) (p=0.000) (Fig. 1B). These indicated that de-escalation of therapy was associated with higher risk of relapse in RA patients although in sustained clinical remission, with DAS28(CRP)>1.82, presence of subclinical synovitis and 2 csDMARDs combination therapy as the risk factors. Therefore, applying de-escalate-therapy strategy in these patients should be cautious.

Discussion

With the proposition of the T2T strategy, along with emerging of new medications, a larger proportion of RA patients are now able to achieve clinical remission, even sustained clinical remission. Given the economic burden and potential side effects of DMARDs, the updated guideline proposed by EULAR has mentioned that de-escalation of therapy can be considered in the patients who are in sustained clinical remission. However, when and how to reduce the therapy remains to be clarified. In our study, RA patients in sustained clinical remission were divided into maintain-therapy group and de-escalate-therapy group according to their treatment adjustment. We found that the relapse rates were similar in the two groups during 1-year follow-up, however, dramatically higher during the 2-year follow-up in the de-escalate-therapy group (52.5% *vs*. 25.7%, p=0.017).

Since a high relapse rate was reported not only in our study, but also in many other studies, several potential risk factors associated with RA relapse have been investigated. The risk factors to predict relapse in our study were DAS28(CRP), presence of subclinical sonographic synovitis, de-escalate-therapy, and 2 csDMARDs combination therapy at baseline. De-escalate-therapy was the independent risk factor for relapse (OR=3.38, p=0.044), which was consistent to the previous study (6). Interestingly, we found that 26 (65.0%) patients who relapsed received 2 csDMARDs at

Table V. The risk factors for predicting RA relapse by multivariate logistic regression analysis.

Parameters	OR (95% CI)	*p*-value
Duration of reaching SCR	0.95 (0.90, 0.99)	0.015
DAS28(ESR)	1.61 (0.59, 4.38)	0.353
DAS28(CRP)	6.97 (1.11, 43.75)	0.038
ACPA positivity	3.11 (0.59, 16.28)	0.180
Subclinical ultrasonic synovitis	3.67 (1.19, 11.36)	0.024
Bone erosion	0.55 (0.17, 1.72)	0.300
Osteophytes	2.06 (0.68, 6.24)	0.202
De-escalate-therapy	3.38 (1.04, 11.02)	0.044
2 csDMARDs use	3.72 (1.14, 12.20)	0.030

SCR: sustained clinical remission; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28(ESR): disease activity score based on 28 joints and ESR; DAS28(CRP): disease activity score based on 28 joints and CRP; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; DMARDs: disease-modifying anti-rheumatic drugs.

baseline, in contrast, only 26 (48.1%) patients who did not relapse were using 2 csDMARDs combination to keep their sustained remission. Univariate logistic regression analysis further revealed that 2 csDMARDs combination therapy was the risk factor of predicting relapse (OR=3.72, p=0.030). Rheumatologists tend to initiate DMARDs combination therapy for patients with more active, or more aggressive disease in clinical practice. This is probably a reason to explain two DMARDs combination as a risk factor to subsequent relapse. These indicated that taking maintain-therapy may be helpful to reduce relapse if the patient needs 2 csDMARDs to keep sustained remission, however with DAS28(CRP)>1.82 or presence of subclinical synovitis. De-escalation of therapy in these patients is probably more feasible after the DAS28(CRP) is getting lower or subclinical synovitis disappears.

APCA positivity has been generally considered as the risk factors for relapse (6, 12-16). Although ACPA positivity (OR=3.16, p=0.095) was not identified as relapse predictors in our study, a higher tendency was observed in patients relapsed than those who did not relapse (92.5% *vs*. 79.6%, p=0.083). Our previous study along with others had proved that subclinical synovitis detected by ultrasound were associated with subsequent bone erosion and disease relapse in RA patients who have reached clinical remission (17-21). We observed consistent result in this study that subclinical ultrasonographic synovitis was the risk factor for predicting RA relapse (OR=3.67, p=0.024).

Beyond our expectations, we found that relapsed patients seemed to have shorter disease duration (31.2 *vs*. 34.6 months, p=0.086) and shorter duration of reaching sustained remission (8.4 *vs*. 13.3 months, p=0.076). Besides, duration of reaching sustained clinical remission seemed to be protective (OR=0.95, p=0.015) for RA relapse. This may be explained by the usual concept that maintain-therapy strategy is often considered for patients who take longer time to reach sustained clinical remission, and as a result, the disease was unlikely to relapse. This explanation could be proved by the longer disease duration (35.2 *vs*. 32.6 months, p=0.317) and longer duration of reaching sustained remission (13.2 *vs*. 8.8 months, p=0.978) in maintain-therapy group of patients compared to those with de-escalation therapy.

Although the updated EULAR guidelines suggest that treatment reduction can be considered when persistent remission is achieved (22), the persistent remission has not been clearly defined. In this study, when DAS28(CRP), presence of subclinical synovitis and 2 csDMARDs combination were included into the ROC curve, we found that maintain-therapy should be recommended in patients with DAS28(CRP)>1.82, presence of subclinical synovitis and two DMARDs combination therapy although they have reached sustained clinical remission for 6 months. Then

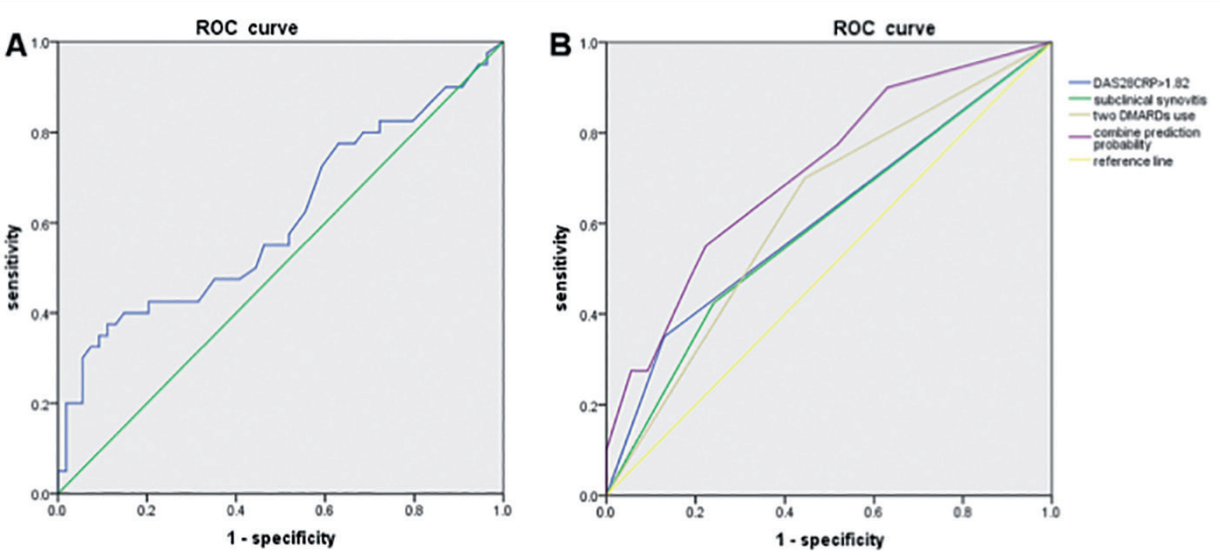

Fig. 1. ROC curve for DAS28(CRP) predicting relapse (**A**) and ROC curve based on logistic regression analysis (**B**).

the question arises how long to keep the maintain-therapy in these patients, until sustained remission to 12 months? We have no definite answer to the question yet at the moment. It is suggested from this study that de-escalation of combination therapy in these patients can be considered when the DAS28(CRP)<1.82 or subclinical synovitis disappears after maintain-therapy for a longer duration.

There are some limitations of this study. First, all the patients enrolled in the study were treated with csDMARDs only. The fact is that very few Chinese patients take biological agents for their maintenance therapy due to economic issues. Second, the principles of de-escalate-therapy strategy in our study were self-defined based on the recommendations for medications used in RA treat-to-target strategy. But as far as we know there is no consensus on how to de-escalate therapy for patients in sustained clinical remission. Finally, some tested parameters in our study did not reach statistical significance, especially the ΔmTSS, is probably due to insufficient sample size or follow-up period. Further study in larger patient cohorts with longer follow-up time to validate our conclusions is needed in the future.

Conclusions

For RA patients who reached sustained clinical remission, de-escalation therapy was associated with higher relapse rate during the 2-year follow-up. De-escalate-therapy strategy should be cautiously considered in these patients who had DAS28(CRP)>1.82, subclinical synovitis with two DMARDs combination therapy.

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