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Predictors of flare in rheumatoid arthritis patients with persistent clinical remission/low disease activity
Data from the TARAC cohort

Sumapa Chaiamnuay, MD[a],* iD, Srisakul Jiemjit, MD[a], Wipatcharin Songdechaphipat, MD[b], Pongthorn Narongroeknawin, MD[a], Rattapol Pakchotanon, MD[a], Paijit Asavatanabodee, MD[a]

Abstract

To identify predictors of rheumatoid arthritis (RA) disease activity flare in RA patients who achieved low disease activity (LDA) or persistent remission from the observational Thai Army Rheumatoid Arthritis Cohort study.

RA patients with persistent clinical remission, defined by disease activity score 28 (DAS28) < 2.6 and LDA defined by DAS28 ≤ 3.2 for 3 consecutive months, were recruited and followed-up for at least 2 years. The flare was defined by an escalation of DAS28 ≥ 1.2 plus their physicians' decision to enhance RA treatment. Differences between sustained remission/LDA and flare groups were analyzed, by Chi-square test and unpaired Student t test. Multivariate Cox proportional hazard regression analysis was conducted to determine flare predictors.

From 199 RA patients, female were 82.9%. Anticitrullinated peptide antibodies (ACPA) or Rheumatoid factor (RF) were found in 69.8% of patients. Flares occurred in 69 patients (34.9%). Multivariate analysis found that the timescale from symptoms emergence to DMARD commencement, the timescale from DMARD commencement to when RA patients showed remission/LDA, the occurrence of RF or ACPA, LDA (in contrast to remission) and the increased DAS28 score when remission/LDA was achieved and tapering DMARDs promptly when persistent remission/LDA was achieved were predictors of RA flares with hazard ratios of (95% confidence interval [CI]) of 1.017 (1.003–1.030), 1.037 (1.015–1.059), 1.949 (1.035–3.676), 1.926 (0.811–4.566), 2.589 (1.355–4.947), and 2.497 (1.458–4.276), respectively.

These data demonstrated that early and aggressive DMARDs treatment approach could maintain remission espcially in seropositive patients. Tapering should be applied minimally 6 months after reaching remission.

Abbreviations: ACPA = anticitrullinated peptide antibodies, ACR = The American College of Rheumatology, DAS28 = disease activity score 28, DMARDs = disease-modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, EULAR = The European Alliance of Associations for Rheumatology, LDA = low disease activity, RAR = rheumatoid arthritis, RFR = rheumatoid factor, TARAC = Thai Army Rheumatoid Arthritis Cohort, TTD = time to start, TTF = time to flare, TTR = time to remission.

Keyword: clinical remission, flares, predictors, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which results in joint pain and permanent joint damage. This leads to disability, impaired quality of life and complications particularly stroke and heart diseases, which are the main causes of premature death. Treatment for RA has been improved during recent decades. There are several novel targeted synthetic and biological disease-modifying antirheumatic drugs (DMARDs) available for treating RA. The American College of Rheumatology (ACR) recommended aimed at low disease activity (LDA) and/or remission as a therapeutic target.[1] However, RA is a fluctuating disease which shows fluctuating disease activity over time, so remission should be sustained over time, so-called sustained or persistent remission.

Recent ACR and the European Alliance of Associations for Rheumatology (EULAR) recommendations for managing RA suggested that once remission is reached, glucocorticoids should be tapered first. Subsequently, if remission continues, reduction of targeted or biological synthetic DMARDs

Key points

- Flares after persistent remission/LDA commonly occurred.
- Early and aggressive DMARDs treatment to reach deep remission can prevent flares.
- Tapering DMARDs approach should be applied after a long stable remission.

is recommended.[1,2] However, tapering DMARDs can lead to a rise in disease activity known as RA flares. RA flare is quite common and about 50% of patients in remission may experience a disease flare within 2 years.[3] Furthermore, RA flares are associated with functional deterioration, radiographic progression and worsening cardiovascular comorbidity.[4–6]

Previous studies have demonstrated that sustained remission only occurs in a minority of RA patients.[7,8] A few studies have examined predictors for post remission flares in RA. Those studies included patients showing clinical and/or ultrasonographic remission.[6,9,10] Subclinical synovitis from ultrasound, shorter duration of remission, functional disability, high disease activity score 28 (DAS 28) and failure to reach 2010 ACR/EULAR remission criteria are the risk factors for flare.[9,11] However, musculoskeletal ultrasound is not universally available, compared with plain radiographs of hands and feet which are normally performed at baseline for all RA patients. Moreover, 1 study investigated flares in RA patients showing LDA which reported that the only predictor for LDA was poor baseline functional status.[12]

This study aimed to examine clinical, radiographic and serological factors which can predict RA flares after reaching persistent remission or LDA in the Thai Army Rheumatoid Arthritis Cohort (TARAC) patients.[13]

2. Materials and Methods

2.1. Patients

Data were obtained from 510 RA patients who were recruited into the TARAC. The TARAC is an observational, real-world cohort of patients with RA recruited at the Rheumatology Clinic, Phramongkutklao Hospital since 1990.[13] Inclusion criteria to the TARAC cohort were patient aged greater than 18 years old and diagnosed RA according to the ACR classification criteria[14] or the 2010 ACR/EULAR classification criteria.[15] Patients were followed every 3 months. All enrolled patients gave their written informed consent. The flow chart of this study is shown in Figure 1.

Inclusion criteria were as follows:

1. RA patients in LDA or persistent remission state by the DAS 28 criteria (DAS 28 < 2.6 or ≤ 3.2, respectively) for more than <3 months [16].
2. Patients had more than 2 years of continuous follow-up treatment following remission or LDA.

Exclusion criteria were patients with RA who had overlapping syndrome, excepting secondary Sjogren syndrome, patients without continuity of treatment, cancer patients and/or those with immunodeficiency disorders, for example AIDS, patients with psychiatric problems, pregnant/breastfeeding patients and patients unable to assess pain including patients with fibromyalgia, polyneuropathy, or neuropathic pain.

2.2. Measurement and data collection

Baseline characteristics were obtained including age, gender, body mass index, alcohol and tobacco usage, and medical comorbidities. The RA characteristics included disease duration, anticitrullinated peptide antibody (ACPA) positivity, rheumatoid factor (RF) positivity, baseline hand radiographic findings, current and previous DMARDs treatments, general health in visual analogue scale, 28 joint counts and erythrocyte sedimentation rate (ESR). The DAS 28-ESR was calculated and documented for each patient at each visit. Serum RF was measured using a quantitative immune turbidimetric assay, and positive results were defined by a value of greater than 14 IU/mL. Laboratory test for measurement of ACPA level has been implemented in Phramongkutklao Hospital since 2007, so some patients who were diagnosed with RA prior to that time never had this blood test. ACPA level was analyzed using second-generation ELISA test (anti-CCP2, Euroimmune, Lübeck, Germany) with cut off value of >5 RU/mL.[17] The significant changes of radiographic hand findings included joint space narrowing and erosions compatible with RA, that were documented in medical records by rheumatologists. The ESR was measured using an ESR analyzer Ves Matic (Diesse Diagnostica Senese, Siena, Italy).[18] Common complications of RA were also obtained and documented. This study was approved by the Royal Thai Army Institutional Review Board (approval number IRBRTA129/2562).

2.3 Definitions

Remission was defined by DAS 28 < 2.6. Low, moderate, and high disease activity states were defined by DAS 28 ≤ 3.2, >3.2 but ≤ 5.1, and > 5.1, respectively.[19]

Persistent remission/LDA was defined by LDA or remission for 3 consecutive months.

Flare was defined by DAS28 definition of flare which was a rise in DAS 28 of ≥1.2 plus physician's decision to adjust treatment to control RA disease activity.[20]

The duration from symptom onset to commencement of DMARDs was defined by time to diagnosis/time to DMARDs (TTD).

The duration from commencement of DMARDs treatment to RA patients entering disease remission/LDA state was defined by time to remission (TTR).

The duration from achieving persistent remission/LDA to RA patients experiencing flare was defined by time to flare (TTF).

2.4. Statistical analysis

Patients were classified into 2 groups: patients who had sustained remission/LDA (sustained remission/LDA group) and those who experienced flares (flare group). The differences of continuous variables between the 2 groups were analyzed by Mann–Whitney U test for non-normally distributed data or independent sample t-testing for normally distributed data. Differences of the categorical variables between the 2 groups were analyzed by Fisher exact test for non-normally distributed data or Chi-square for normally distributed data. Univariate and multivariate Cox proportional hazard regression analysis was conducted to determine the predictors of flare. The results were shown as hazard ratio (HR) with 95% CI. The level of statistical significance was *P* value < .05. All statistics were performed using STATA, version 12.0. The multiple imputation method was implemented to handling missing variables.

3. Results

There were 510 RA patients in the TARAC. They were regularly followed in the Rheumatology Outpatient Clinic, Department of Medicine, Phramongkutklao Hospital from January 1996 to December 2019. One hundred ninety-nine patients had been in states of persistent disease remission/LDA and had a follow-up time of at least 2 years after achieving persistent remission/LDA. Three hundred one patients were excluded due to the following
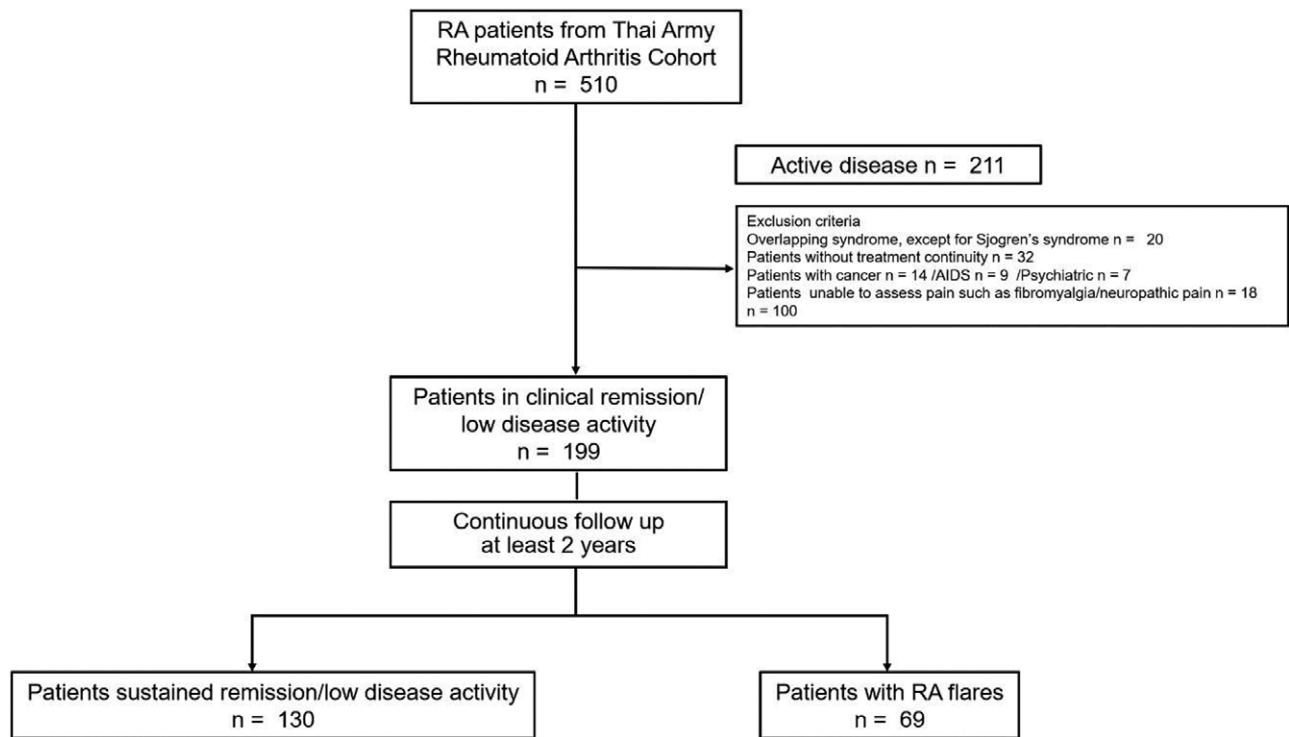
Figure 1. Process of recruitment.

Table 1

Baseline characteristics, comorbidities, and radiographic findings of rheumatoid arthritis patients between patients had who sustained remission or low disease activity and those who had flares after achieving remission or low disease activity.

Characteristics	Sustained remission/ low disease (n = 130)	Flare (n = 69)	P value
Demographics and social history (n, %)			
Age, yr (mean ±SD)	52.68 ± 11.87	51.01 ± 11.8	.347
Female	107 (82.3)	58 (84.0)	.755
Tobacco use	2 (1.5)	7 (10.1)	.004
Alcohol use	2 (1.5)	3 (4.3)	.211
Serology (n, %)			
Positive RF	79 (62.7)	55 (79.7)	.014
Positive ACPA*	49/90 (54.4)	31/42 (73.8)	.037
Positive RF or ACPA	83 (63.8)	56 (81.2)	.037
Extra-articular manifestations (n, %)			
Rheumatoid nodule	42 (32.3)	20 (28.9)	.626
Interstitial lung disease	1 (0.7)	2 (2.8)	.241
Sicca symptom	13 (10)	14 (20.2)	.044
Comorbidities (n, %)			
Diabetes miletus	16 (12.3)	6 (8.6)	.439
Hypertension	58 (44.6)	27 (39.1)	.457
Dyslipidemia	56 (43.0)	30 (43.4)	.384
Ischemic heart disease	2 (1.5)	2 (2.8)	.515
Osteoporosis	13 (10.0)	12 (17.3)	.134
Radiographic findings at baseline (n, %)			
Juxta-articular osteopenia	75 (57.6)	51 (73.9)	.036
Joint space narrowing	53 (40.7)	46 (66.7)	.001
Marginal erosions	31 (23.8)	20 (29.0)	.447

ACPA = anticitrullinated peptide antibody, RF = rheumatoid factor, SD = standard deviation.
*Tested in 132 patients: 90 patients in sustained remission/low disease activity group and 42 patients in flare group.

reasons: 211 patients had active disease, 20 patients had overlapping syndrome except for secondary Sjogren syndrome, 32 patients were lost follow-up, no treatment continuity or not enough time for follow-up after achieving persistent remission/LDA, 14 patients had cancer, 9 patients had acquired immune deficiency syndrome, 7 patients had concomitant psychiatric disorders and 18 patients had other causes of pain such as fibromyalgia and neuropathic pain. Of 199 patients, 165 patients (82.9%) were female, 144 patients (72.4%) were tested positive for either RF or ACPA and mean (SD) disease duration was 7.1 (3.7) years.

Sixty-nine patients (34.6%) experienced RA flares and 130 patients had no flares within 2 years after achieving persistent remission/LDA. In the flare group, the mean (SD) TTF was 10.0 (4.2) months.

The demographics, serologies, comorbidities, and baseline radiographic findings were shown in Table 1. There were no differences in age, gender, and comorbidities between groups. There were more patients in the flare group who used tobacco than those in the sustained remission/LDA group (10.1% vs 1.5%, $P = .004$). There were more patients in the flare group who had RF or ACPA and sicca symptoms than those in the sustained remission/LDA group (81.2% vs 63.8%, $P = .037$ and 20.2% vs 10.0%, $P = .044$, respectively). In terms of baseline radiographic findings, there were more patients in the flare group who had juxta-articular osteopenia and joint space narrowing than those in the sustained remission/LDA group (73.9% vs 57.6%, $P = .036$ and 66.7% vs 40.7%, $P = .001$, respectively). There was no difference in the presence of marginal erosion on baseline hand radiographs between 2 groups.

The medications used at the time of RA diagnosis and at the time of persistent remission/LDA were presented in Table S1, Supplemental Digital Content, http://links.lww.com/MD/G958. All patients were prescribed DMARDs. Methotrexate was the most prescribed DMARD in both groups at both times. Prednisolone was prescribed in approximately one-third of patients in both groups at both times. There were no differences in medication prescribed between groups.

The durations, disease activity scores and tapering strategies were shown in Table 2. The proportion of the patients who had achieved remission (DAS 28 < 2.6) at the time of entering persistent remission/LDA state was higher in the sustained remission/LDA group than those of the flare group (48.5% vs 31.9%, P = .035). The means (SD) of TTD and TTR were significantly longer in the flare group than those in the sustained remission/LDA group (18.4 [21] vs 10.1 [10.0], P = .003 and 23.4 [11.6] vs 14.8 [8.5], P < .001, respectively).

For the DAS28 score, the flare group had higher disease activity score at the time of RA diagnosis and at the time of achieving persistent remission/LDA than those of the sustained remission/LDA group with the means (SD) of 5.6 (1.1) versus 5.3 (1.3) and 2.7 (0.4) versus 2.5 (0.4) and P value of 0.032 and 0.017, respectively. Six months after achieving persistent remission/LDA, the DAS 28 score increased in the flare group with the mean (SD) of DAS28 in the flare group higher than that in the sustained remission/LDA group (3.50 [0.65] vs 2.72 [0.61], P value < 0.001).

There was a higher proportion of patients in the flare group than those in the sustained remission/LDA group who received DMARDs tapering strategy immediately at the time of achieving persistent remission/LDA (29% vs 8%, P < .001). However, there was no difference in the proportion of patients with DMARD tapering strategy after achieving persistent remission/LDA between both groups. In addition, there were no differences in the proportion of patients with glucocorticoid tapering strategies at and after the time of achieving persistent remission/LDA between both groups. Overall, DMARDs and glucocorticoid tapering strategies were implemented in two-thirds and one-third of patients in both groups after achieving persistent remission/LDA. In the subgroup analyses of patients who had DMARDs and glucocorticoid tapering strategies, the DAS28 score at the time of DMARDs and glucocorticoid tapering were higher in the flare group than those in sustained remission/LDA group with the means (SD) of 3.0 (0.7) versus 2.5 (0.5) and 3.1 (0.6) versus 2.5 (0.5) and P values of <.001 and <.001, respectively.

The univariate Cox proportional hazard regression analyses found that the RA flare was associated with higher DAS28 at the time of RA diagnosis, longer TTD and TTR, tobacco usage, the presence of RF or ACPA, the presence of sicca symptoms, the presence of joint space narrowing at baseline hands radiographs, LDA (as compared to remission), higher DAS 28 score at the time of remission/LDA and tapering DMARDs immediately at the time of achieving persistent remission/LDA. For categorical variables, the cumulative survivals for

sustained remission/LDA based on stratification by predictive factors were depicted in Figure 2.

The multivariate Cox proportional hazard regression analyses found that TTD, TTR, the presence of RF or ACPA, LDA (as compared to remission), and tapering DMARDs immediately at the time of achieving remission/LDA were the predictors for RA flares with the HRs (95% CI) of 1.017 (1.003–1.030), 1.037 (1.015–1.059), 1.949 (1.035–3.676), 1.926 (0.811–4.566), and 2.497 (1.458–4.276), respectively. In another model substituting LDA (as compared to remission) with DAS28 score, the predictors for RA flares remained unchanged. Additionally, the higher DAS28 score at the time of persistent remission/LDA increased risk of RA flares with the HR (95% CI) of 2.589 (1.355–4.947). The univariate and multivariate Cox regression analyses were depicted in Table 3.

4. Discussion

The study included 199 established RA patients who achieved persistent remission/LDA. After 2 years of follow-up, approximately one-third of patients had flares. This study found that the predictors for RA flares comprised of longer TTD and TTR, sero-positivity (RF or ACPA), failure to achieve remission (DAS 28 > 2.6), a high DAS28 score at the time achieving persistent remission/LDA and immediately tapering DMARDs after achieving persistent remission/LDA.

Although definitions of remission and flares are varied, the rate of RA flare (34%) in this study was quite comparable with other real-life cohorts which showed between 26% and 39% within 1 to 2 years after reaching persistent remission.[6,9,12] The British Early Rheumatoid Arthritis Study (ERAS) showed that sustained clinical remission of 5 years using conventional DMARDs was only 11%.[7]

This study found that the longer TTD significantly predicted more flares after persistent remission/LDA which was consistent with the data from the early arthritis cohorts including the Leiden Early Arthritis Clinic (EAC), the ERAS, the Canadian Early Arthritis Cohort (CATCH) and the trial of early RA in the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo).[21–23] Every 1-month delay of initiating DMARDs can increase a risk of flare by 1.7%. A systematic review reported that symptom duration prior to DMARDs was independently associated with lower probability of reaching DMARD-free sustained remission by 1.1% for each week rise in symptom duration.[24]

The TTR is also noteworthy. Data from the Nijmegen RA Inception Cohort showed the median time of remission were

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Table 2

Durations, disease activity scores and tapering strategies between sustain remission/low disease activity and flare group.

Variables	Sustained remission/low disease (n = 130)	Flare (n = 69)	*P* value
Number of patients DAS28 ≤ 2.6 at remission/low disease activity (n, %)	63 (48.5)	22 (31.9)	.035
Durations			
Time to DMARDs (mo, mean, ± SD)	10.1 ± 10.0	18.4 ± 21.0	.003
Time to remission (mo, mean ± SD)	14.8 ± 8.5	23.4 ± 11.6	<.001
Time to flare (mo, mean ±SD)	50.6 ± 18.9	10.0 ± 4.2	<.001
DAS 28			
At diagnosis (mean ±SD)	5.32 ± 1.03	5.67 ± 1.16	.032
At remission/LDA (mean± SD)	2.58 ± 0.46	2.73 ± 0.41	.017
6 mo after remission/LDA (mean ±SD)	2.72 ± 0.61	3.50 ± 0.65	<.001
At the time of prednisolone tapering (mean± SD)	2.50 ± 0.57 (n = 42)	3.15 ± 0.64 (n = 21)	<.001
At the time of DMARDs tapering (mean ± SD)	2.55 ± 0.58(n = 80)	3.04 ± 0.72 (n = 43)	<.001
Medication tapering at/after achieving remission/LDA			
Decrease DMARDs immediately at the time of achieving persistent remission/LDA (n, %)	11 (8.5)	20 (29.0)	<.001
Decrease DMARDs after achieving persistent remission/LDA (n, %)	80 (62.0)	43 (63.2)	.867
Decrease prednisolone immediately at the time of achieving persistent remission/LDA (n, %)	16 (12.3)	13 (18.8)	.291
Decrease prednisolone after achieving persistent remission/LDA (n, %)	42 (32.3)	21 (30.4)	.873

DAS28 = disease activity score 28, DMARDs = disease-modifying antirheumatic drugs, SD = standard deviation, LDA = low disease activity.
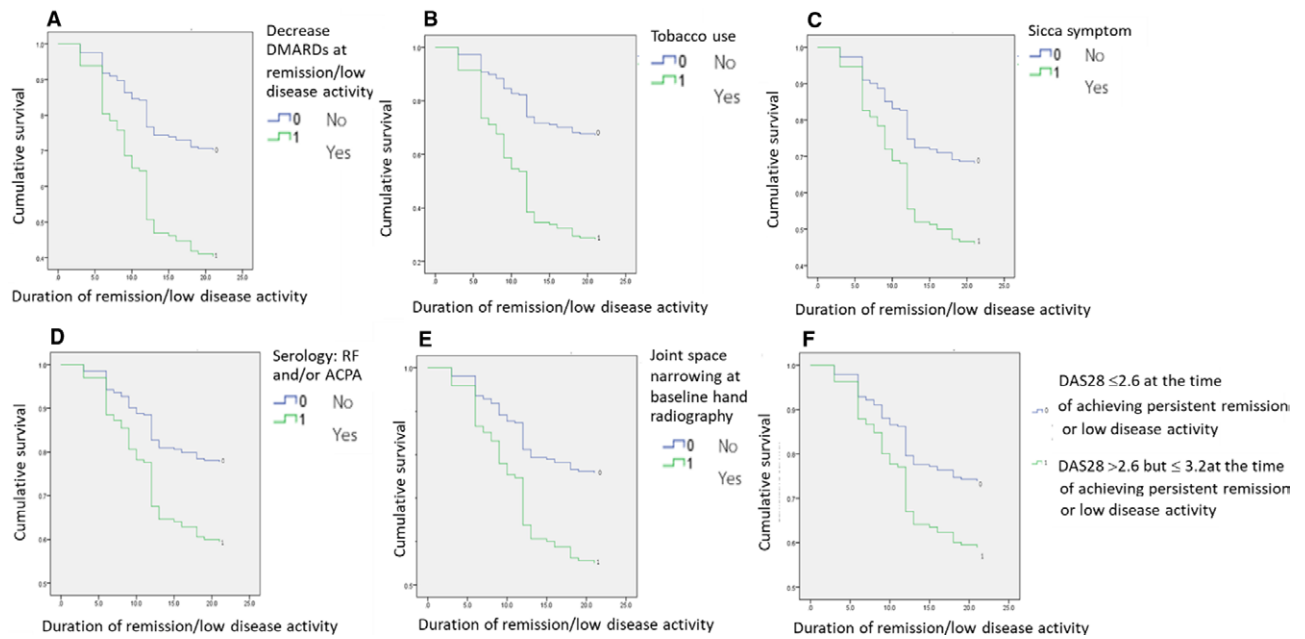
Figure 2. Kaplan–Meier survival curves for cumulative sustained remission/LDA rates stratified by (A) decreasing DMARDs immediately after achieving remission/LDA, (b) tobacco use, (C) Sicca symptoms, (D) the presence of rheumatoid factor or anti CCP antibodies, (E) the presence of joint space narrowing in baseline hand radiographs, and (F) achieving DAS 28 remission. DAS 28 = disease activity score 28, DMARDs = disease-modifying antirheumatic drugs, LDA = low disease activity.

Table 3

Predictive factors for flares in rheumatoid arthritis patients after they achieved persistent remission or low disease activity (univariate and multivariate Cox regression model).

	Univariate			Multivariate		
Clinical characteristics	HR	95% CI	P value	HR	95% CI	P value
At diagnosis of rheumatoid arthritis						
Tobacco use	3.184	0.143–0.688	.004	1.926	0.811–4.566	.137
Positive RF or ACPA	2.067	1.108–3.856	.023	1.949	1.035–3.676	.039
X-ray finding joint space narrow	2.159	0.280–0.764	.003	1.091	0.601–1.984	.773
Sicca symptoms	2.024	0.264–0.888	.018	1.519	0.803–2.932	.207
Time to DMARDs	1.024	1.012–1.037	<.001	1.017	1.003–1.030	.013
Time to remission/ LDA	1.047	1.028–1.066	<.001	1.037	1.015–1.059	.001
DAS 28	1.238	1.007–1.522	.043	1.183	0.956–1.463	.122
At remission/low disease activity of rheumatoid arthritis						
Decrease DMARDs immediately after persistent remission/LDA	2.557	0.232–0.658	<.001	2.497	1.458–4.276	.001
DAS 28						
Model 1: ≤ 2.6 VS > 2.6 - <3.2	1.751	0.344–0.948	.030	1.926	1.112–3.289	.017
Model 2: DAS28	2.029	1.113–3.700	3.700	2.589	1.355–4.947	.004

HR = hazard ratio, CI = confidence interval, RF = rheumatoid factor, ACPA = anticitrullinated peptide antibody, DMARDs = disease-modifying antirheumatic drugs, DAS28 = disease activity score 28, LDA = low disease activity.

lower in patients with sustained remission than patients without it (median time of 9 vs 13 months, $P < .001$). There were 1.11 increased odds of sustained remission, if the first remission was reached 1 month earlier (compared with reaching the first remission 1 month later), 1.37 increased odds to remain in remission, if remission is reached 3 months earlier, and for 1 year earlier remission the odds to remain in remission rose to 3.5.[25] Similarly, this study found that every 1-month delay to achieve remission/LDA can increase the risk of flare by 3.7%. Hence, these observations implied the importance of early diagnosis and treatment as well as achieving remission with any treatment strategy as early as possible in the course of the disease.

RF and ACPA are well-recognized as poor prognostic factors in RA. They were associated with absence of remission and radiographic progression.[26] RF and ACPA have never been reported to predict flares in patients with persistent remission in a real-life cohort of RA patients. However, ACPA was associated with flares in the RCT of RA patients starting tapering strategy.[27] We performed the multivariate Cox regression analyses model using the presence of RF as a substitution for the presence of RA or ACPA. The presence of RF also significantly predicted flares after achieving persistent remission/LDA with HR (95% CI) of 1.92 (1.062–3.497). The presence of ACPA alone was not entered into the model since only 132 patients were tested for it.

Clinical remission has consistently demonstrated better outcomes including deformities, radiographic progression, mortality as well as patient-reported outcomes than LDA.[28,29] This study has added to the current knowledge that LDA increased

flares as compared to remission. We found that for every one-point increase of DAS28, there was a 2.6-fold rise in the probability of flares after achieving persistent remission. In the RCTs, that examined withdrawal of antitumor necrosis factor agents or dose reduction in RA patients who had clinical remission, it was found that patients who had sustained deep remission, defined by DAS28 ≤ 1.98 on 2 consecutive visits, were more likely to retain remission after anti-TNF agents dose reduction.[30,31] Altogether, the lower the DAS 28 score or the deeper remission, the lower chance of future flares.

Considerable RCTs and systematic reviews have reported that reduction of biologic and synthetic DMARDs could result in flares for many patients and so should be cautiously done to adhere with the Tight Control and Treat-to-Target principles.[32–36] Biologic and synthetic DMARDs were recommended to steadily taper throughout discontinuation after achievement of persistent remission.[2] Nevertheless, a definition for the term "persistent" remission remains inconclusive. No study examined whether tapering DMARDs after 3, 6, or 12 months of stringent remission had any different outcomes. This study revealed that tapering DMARDs immediately after achieved persistent remission/LDA or 3 months after entering remission/LDA increased 2.5-fold risk for RA flares. However, tapering DMARDs after achievement of persistent remission/LDA lead to no difference in RA flares between flare and sustained remission/LDA groups, suggesting that a better time to start tapering DMARDs should be at least 6 months after entering remission/LDA.

This study has some limitations. First, RA patients in the TARAC are established RA patients, not early arthritis patients, so the disease durations were quite long. Furthermore, ACPA testing became available in our hospital in 2010, so the results were not available in all patients. Although remission is the target as many expert societies recommend by, it is quite difficult to reach in a cohort of established RA patients.[2,37,38] Persistent remission was achieved in only 85 patients in this cohort. According to the recent EULAR 2019 recommendations, LDA constitutes an alternative goal, especially in patients with longstanding disease. Hence, we decided to enroll patients with either persistent remission or LDA. Second, ultrasonographic findings, which included the presence of gray-scale synovial hypertrophy and power-Doppler activity were reported as associated with flares in RA patients who had remission.[9] These ultrasonographic findings were not collected and not available in the present study. Third, patient-reported outcomes were found in several studies which predicted flares after remission,[12,34] although they were not routinely recorded in the TARAC and were not examined in this study.

5. Conclusions

This study found flares after persistent remission/LDA were quite common. Predictors for RA flares after persistent remission/LDA were duration from onset symptoms to DMARDs initiation; duration from RA diagnosis to remission/LDA; the presence of RF or ACPA; higher DAS28 score at the time of achieving remission/LDA and tapering DMARDs at the time or immediately after achieving remission/LDA. These results emphasized on early and intensive DMARDs treatment to achieve remission. The lower DAS28 score at remission contributes to reducing flares. Tapering DMARDs strategies should be implemented after a long stable remission and should be particularly cautious in RA patients with RF or ACPA.

Author contributions

SC and SJ were involved in the conception of the study, performed the analyses, drafted the manuscript, and revised the manuscript. WS and SJ collected data. The other authors assisted in interpretation of the results from the analyses and drafting the manuscript. All authors have read and approved the final manuscript.

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