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ORIGINAL ARTICLE

Predictors and the optimal duration of sustained remission in rheumatoid arthritis

Sibel Yilmaz-Oner[1] · Ummugulsum Gazel[1] · Meryem Can[1] · Pamir Atagunduz[1] · Haner Direskeneli[1] · Nevsun Inanc[1]

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Abstract

Objective To determine predictors and optimal duration of sustained remission (SR) in patients with rheumatoid arthritis (RA).

Methods A total of 428 consecutive patients with RA visiting our clinic routinely between 2012 and 2013 were evaluated. Seventy seven of these patients in DAS28 remission were enrolled and followed up for 62.2 ± 9.9 months. Patients in remission ≥ 6 months (SR) and shorter (non: N-SR) were compared in terms of demographic-clinical data and the psychosocial factors. At enrollment, 1st and 5th years, patients in DAS28, SDAI, and Boolean remission were determined.

Results Sixty three patients were in SR and 14 in N-SR. Lower baseline DAS28 and HAQ scores, anti-CCP were positive predictors of SR. Although the presence of anxiety, depression, fibromyalgia, and fatigue were lower in the SR group, there was no significance. Patients in DAS28 remission (100%) at baseline reduced to 64% at 1st and 42.6% at 5th years. Patients satisfying SDAI and Boolean remission at these three visits were 49%, 44%, and 32.4% vs 41%, 28%, and 20.6%, respectively. If the duration of remission is defined as 6 months, the remission rates of SDAI at inclusion and fifth years' visits were similar but Boolean remission rates differed significantly and if it is accepted as ≥ 12 months, both the SDAI and Boolean remission rates were not different.

Conclusion Low DAS28 and HAQ scores at baseline, anti-CCP were positive predictors of SR. Instead of 6 months, remission duration for ≥ 12 months would probably help us to predict SR independently from the chosen criteria; Boolean or SDAI.

Keywords ACR/EULAR definition of remission · Disease activity score · Predictors · Rheumatoid arthritis · SDAI · Sustained remission

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes severe adverse outcomes as joint destruction, physical disability, lower quality of life, and shortened life expectancy compared with general population [1, 2].

The management of RA has been changed during the past decades and especially after the introduction of biologic drugs. The current treatment strategy is reaching a status of clinical remission to improve outcomes in patients with RA [3]. Treating to target strategies, earlier combinations of synthetic disease modifying anti-rheumatic drugs (DMARDs) and more aggressive treatment of patients with poor prognostic factors have made the remission an achievable treatment goal.

In the 2016 European League Against Rheumatism (EULAR) updated recommendations for the management of RA, it is reported that target state should be sustained remission or low disease activity even though the definition of the term "sustained" is not available yet [4]. Sustained remission (SR) should be the ultimate goal of RA treatment to halt joint damage and prevent the accrual of disability [5]. Increased full physical function prevalence as much as normal population and ongoing improvement in physical function over time are shown in RA patients with sustained remission [6, 7].

Several definitions of remission are available to assess various aspects of RA and treatment response. These composite indices are derived from multiple individual variables including clinical and laboratory data and physician and patient global assessments (PGA, PtGA). In literature, there are studies indicating the impacts of comorbidities on achieving remission via affecting the outcome measures and disease

✉ Sibel Yilmaz-Oner
sibely113@gmail.com

[1] Medical Faculty, Department of Rheumatology, Marmara University, Pendik, 34890 Istanbul, Turkey

activity [8]. Multimorbidity, measured by Rheumatic Disease Comorbidity Index, is used for patients with RA carrying physical comorbidities and depression [9]. On the other hand, the PtGA may be influenced by non-inflammatory comorbidities as pain, fibromyalgia, depression, anxiety, accrued joint damage, or others [10–14] and is criticized as the limiting factor to achieve remission of RA [12].

In EULAR recommendations, it is also reported that in patients with persistent remission tapering biologic DMARDs/conventional synthetic DMARDs can be considered [4]. In recent years, there are studies reporting DMARD-free sustained remission in RA as an achievable goal with the advantages of early and intensive therapy [15, 16]. Based on this data, factors predicting sustained remission are essential to individualize treatment, guide therapeutic decisions, and recognize patients that have an opportunity to taper treatment in daily practice [16, 17]. Until now, the predictors of sustained remission in RA, including demographics, functional status, clinical features, and medications, have been investigated [18–21]. However, most studies included patients with early RA and there are very few studies focused on sustained remission in established RA.

The objective of our study was to evaluate possible baseline predictors and optimal duration of sustained remission in patients with established RA and comparison of its predictability in between different remission criteria. In addition, the secondary aim was to investigate the effects of anxiety, depression, fibromyalgia, and fatigue on sustained remission.

Materials and methods

A total of 428 consecutive patients with RA of our ongoing observational cohort, visiting outpatient clinic routinely between September 2012 and 2013, were evaluated. Seventy seven of these patients fulfilling the DAS28 remission (< 2.6) were enrolled to the study (first visit for each patient) and followed up prospectively for 62.2 ± 9.9 months. Patients were treated in our outpatient clinic according to standard of care and evaluated at least two times in a year with routine assessments from 2012 to 2017. Duration of remission was calculated as time between the enrollment visit and the subsequent first visit with the DAS28 score ≥ 2.6. Of these patients who fulfilled the DAS28 remission criteria on at least two consecutive assessments at a ≥ 6 month time interval in 12 months were defined as in sustained remission (SR) and the others achieving DAS28 remission criteria at only one timepoint or occasionally but not sustained overtime were categorized as having "non-sustained remission" (N-SR). In addition, an alternative description of sustained remission with a fulfillment of DAS28 remission in two consecutive assessments at ≥ 12 month time period was also evaluated for the performance to determine the sustainability of remission.

All patients were older than 18 years and fulfilled the 1987 American College of Rheumatology criteria for RA [22]. Written informed consent was obtained from all patients and the study was approved by the Marmara University School of Medicine Ethics Committee for Clinical and Laboratory Research (the approval number was 09.2012.0208).

The variables collected at the enrollment visit included patients' gender and age, comorbidities, disease duration, extra-articular manifestations, time to onset of treatment after first symptoms, DMARD, glucocorticoid and/or biologic use, levels of rheumatoid factor (RF) and antibodies against cyclic citrullinated proteins (anti-CCP), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, tender and swollen joint counts of 28 joints (TJC, SJC), and degree of disability assessed by Health Assessment Questionnaire (HAQ) [23], PGA, and PtGA on a visual analogue scale (VAS) of 10 cm. Patients were evaluated for the presence of anxiety and depression with the Hospital Anxiety and Depression Scale (HADS) [24], fibromyalgia (FM) with the American College of Rheumatology 2010 preliminary criteria [25], and fatigue with the Multidimensional Assessment of Fatigue Scale (MAF) [26] as reported in our previous report [13].

At the initial visit, approximately first year (14.7 ± 5.3 months) and fifth (62.2 ± 9.9 months) years, the remission rates of patients were determined by the DAS28 (< 2.6) [27, 28], Simple Disease Activity Index (SDAI) ≤ 3.3 (the sum of the number of swollen and tender joints, CRP [mg/dL], PGA, and PtGA) [29] and Boolean-based ACR/EULAR remission criteria (Boolean Cr) (the tender and swollen joint counts ≤ 1, PtGA ≤ 1 cm on a VAS of 10 cm and CRP ≤ 1 mg/dL) [30]. Patients in sustained and non-sustained remission groups were compared with each other in terms of baseline demographic, clinical, disease-related features and the presence of anxiety, depression, fibromyalgia, and fatigue to determine the effects of non-inflammatory confounders on sustained remission. During the follow-up, the number of visits fulfilling the DAS28 remission criteria and the mean remission visit ratio (the ratio of remission visits to total visits) of patients were calculated. Individuals in DAS28, SDAI, and Boolean remission at first visit were compared with regard to the number of DAS28 remission visits throughout the follow-up period. We also assessed the difference of remission rates according to DAS28, SDAI, and Boolean remission criteria at initial, first, and fifth years' visits.

Statistical analysis

Descriptive statistics were reported as medians (min-max) and mean ± SD for continuous variables and as frequencies (percentage) or counts as categorical data. Comparisons between sustained remission and non-sustained remission groups with regard to baseline features of patients were

analyzed using Student's *t* or Mann Whitney *U* tests for continuous and the chi-square test for categorical variables. Mc Nemar's test was used for comparisons between the related groups. All analysis of inclusion and first-year visits were done with 77 patients' data. Twelve patients were excluded from analysis of the fifth year since they were lost to follow-up after the first year's evaluation.

Statistical analyses were performed by using the Software Statistical Package Sciences (SPSS) for Windows version 16.0. Level of significance was $p < 0.05$.

Results

The mean age of the 77 patients was 51.6 ± 1.2 years and 41 were women. Mean disease duration was 11.2 ± 8 years, and 53 (68.8%) and 49 (59.7%) of patients were seropositive for RF and anti-CCP, respectively. Twenty patients (25.9%) were on biological agents (alone or combination with DMARDs), 32 (41.6%) were receiving corticosteroids, and 75 (97.4%) were on DMARDs at inclusion visit. During the follow-up, until the study enrollment, the biological treatments administered were etanercept, 13 (16%); rituximab, seven (9%); infliximab, 11 (14%); adalimumab, nine (11%); abatacept, one (1.2%), and tocilizumab, one (1.2%). In this period, five patients had received three different biologics and the other five patients were administered two separate biological agents. There was no difference between anti-CCP positive and negative patients with regard to receiving biological DMARDs according to the data of enrollment visit.

Of these patients, 63 were in SR and 14 in N-SR groups (Table 1). Twenty-four (42.8%) of 56 patients in the SR group were still in DAS28 remission at five years visit (Table 2). The results of comparisons between the SR and N-SR groups with regard to baseline demographic, clinical, and laboratory data were summarized in Table 1. Lower baseline DAS28 and HAQ scores ($p = 0.045$; $p = 0.026$, respectively) and anti-CCP positivity ($p = 0.035$) were positive predictors of SR. Although the presence of anxiety, depression, fibromyalgia, and fatigue were lower in the SR group, there was no statistical significance between the two groups (Table 1).

Patients meeting the DAS28 criteria at the initial visit (n = 77; 100%) reduced to 64% ($n = 50$) at the first and 42.6% (n = 29) at the fifth year. The percentage of patients satisfying SDAI and Boolean criteria at the initial, first-year, and fifth-year visits were 49%, 44%, 32.4% ($n = 22$) vs 41%, 28%, 20.6% ($n = 14$), respectively (Fig. 1).

The mean remission visit ratio (the ratio of remission visits to total visits) of patients' in the SR group was 0.57 ± 0.28, and it was significantly different than the N-SR group (0.35 ± 0.24; $p = 0.036$). The number of visits fulfilling the DAS28 remission criteria was similar in patient groups with Boolean ($n = 32$) and DAS28 (n = 77) remission (5.7 ± 3.2 vs 5.4 ± 3.1; $p = 0.995$). Similarly, no difference was found between patients in SDAI ($n = 38$) and DAS28 remission (5.6 ± 3.3 vs 5.4 ± 3.1; $p = 0.769$).

If the duration of remission is defined as 6 months, the remission rates of SDAI at inclusion and fifth years' visits were similar but Boolean remission rates differed significantly and if it is accepted as ≥ 12 months, both the SDAI and Boolean remission rates were not different (Table 2).

Discussion

In our observational study, 63 patients were in SR and 14 were in N-SR and if the duration of remission is defined as ≥ 12 months; 29 of our patients were in SR and 36 in N-SR. A shorter disease duration, lower baseline disease activity score, younger age, male gender, a shorter time to remission, lower baseline functional impairment, and methotrexate co-prescription with anti-TNF (anti-tumor necrosis factor) therapies are several baseline demographic and clinical factors reported as predictors of SR in patients with RA [18–20, 31, 32]. Moreover, in a recent study from Spain, Valor et al. reported DAS28, the presence of Doppler USG synovitis, RF, and a smoking habit as the predictors of long-term tapered biological DMARD failure in patients with RA in sustained remission [21]. A low DAS28 score and good functional ability were positively associated with sustained remission in our study which was in line with previous reports [33]. The relationship between anti-CCP positivity and sustained remission is still a debating issue in the literature. Castrejón et al. showed that absence of RF, anti-CCP, or radiographic erosions did not predict remission at 6 and/or 12 months in a French early arthritis cohort [34]. The absence of anti-CCP and RF was not among the predictors of sustained DAS28 and Boolean remission in another study from Argentina [35]. On the other hand, sustained remission is reported less prevalent in anti-CCP positive patients and more prevalent in patients commencing DMARD therapy earlier [36, 37]. We found anti-CCP positivity more common in the SR group and hypothesize that seropositivity of patients could provide clinicians and patients the possibility of early and intensified antirheumatic therapy in the "window of opportunity". It has been shown that the median time to remission is shorter in patients with SR and longer time between the onset of symptoms and initiation of DMARDs is associated with a decreased chance to achieve sustained remission [31, 37].

In RA, the composite indices may be insufficient to assess reduction in inflammatory activity because of components, especially PtGA which is reported high in patients with depression, FM, and fatigue [10–13, 38–41]. To date, levels of many inflammatory markers have been assessed in RA to be able to distinguish inflammatory and non-inflammatory sources of high composite scores [42, 43]. Kekow et al. showed that significantly more patients achieved clinical

Table 1 Comparison of baseline demographic and clinical characteristics of patients with rheumatoid arthritis in sustained or non-sustained remission according to DAS28

	Patients in sustained remission ($n = 63$)	Patients in non-sustained remission ($n = 14$)	p
Basal DAS28, mean ± SD	2 ± 0.4	2.2 ± 0.3	*0.045*
Basal HAQ (0–3)	0.3 ± 0.5	0.5 ± 0.4	*0.026*
RF (+), *n* (%)	49 (66.3)	7 (50)	0.930
Anti-CCP (+), *n* (%)	41 (65)	5 (35.7)	*0.035*
Basal CRP (+), *n* (%)	7 (11.1)	4 (28.5)	0.091
Basal ESR (mm/h), mean ± SD	13 ± 7.8	16.6 ± 7.5	0.850
Age, mean ± SD, years	51.3 ± 12.5	52.9 ± 10.5	0.647
Female, *n* (%)	41 (65.0)	11 (78.5)	0.329
Comorbidities	30 (50.6)	8 (57.1)	0.530
Time to onset of treatment in months, mean ± SD	15.6 ± 26.9	32.6 ± 51	0.536
DMARD1 (+), *n* (%)	51 (80.9)	13 (92.8)	0.442
DMARD2 (+), *n* (%)	35 (55.5)	7 (50.0)	0.706
Biologic DMARDs (+), *n* (%)	18 (28.5)	2 (14.2)	0.270
Extra-articular manifestations, *n* (%)	14 (22.2)	4 (28.5)	0.907
SDAI, mean ± SD	3.6 ± 2.8	4.3 ± 2.3	0.396
PGA, mean ± SD	0.8 ± 0.8	1.1 ± 0.8	0.145
PtGA, mean ± SD	1.7 ± 1.8	2.1 ± 1.2	0.253
SJC, mean ± SD	0.1 ± 0.4	0.3 ± 0.8	0.687
TJC, mean ± SD	0.3 ± 1	0.1 ± 0.5	0.470
Disease duration, mean ± SD (years)	10.3 ± 7.3	15.1 ± 9.9	0.117
Boolean rem, *n* (%)	28 (44.4)	4 (28.5)	0.276
SDAI rem, *n* (%)	33 (52.3)	5 (35.7)	0.259
Anxiety (+), *n* (%)	9 (14.2)	4 (28.5)	0.197
Depression (+), *n* (%)	13 (20.6)	4 (28.5)	0.517
Fibromyalgia (+), *n* (%)	6 (9.9)	2 (14.2)	0.597
Fatigue (GFI), mean ± SD	13.2 ± 12.5	16.9 ± 12.8	0.251

Level of significance was $p < 0.05$

DMARD1-DMARD2 disease-modifying anti-rheumatic drug 1 (methotrexate, leflunomide) -2 (sulfasalazine, hydroxychloroquine), *PGA* physician global assessment, *PtGA* patient global assessment, *SJC* swollen joint count, *TJC* tender joint count, *GFI* Global Fatigue Index

remission at week 104 if anxiety/depression symptoms were absent at baseline [44]. Nevertheless, none of the studies have presented the data on the relationship between possible psychosocial confounders and SR in the literature [32]. Therefore, we aimed to evaluate potential effects of anxiety, depression, FM, and level of fatigue on SR and found these non-inflammatory complaints more among patients in non-sustained remission group.

Table 2 Remission status of patients according to DAS28, Boolean, and SDAI criteria at inclusion and fifth years' visits in groups with sustained remission for 6 and 12 months

Remission groups/criteria		Patients in remission at initial visit (%, *n*)	Patients in remission at fifth year's visit (%, *n*)	p
Patients in sustained remission ≥ 6 months ($n = 56$)	DAS28	100 (56)	42.8 (24)	
	SDAI	48.2 (27)	37.5 (21)	0.216
	Boolean	41.0 (23)	23.2 (13)	0.001
Patients in sustained remission ≥ 12 months ($n = 29$)	DAS28	100 (29)	51.7 (15)	
	SDAI	62.0 (18)	41.3 (12)	1.000
	Boolean	51.7 (15)	31.0 (9)	0.267

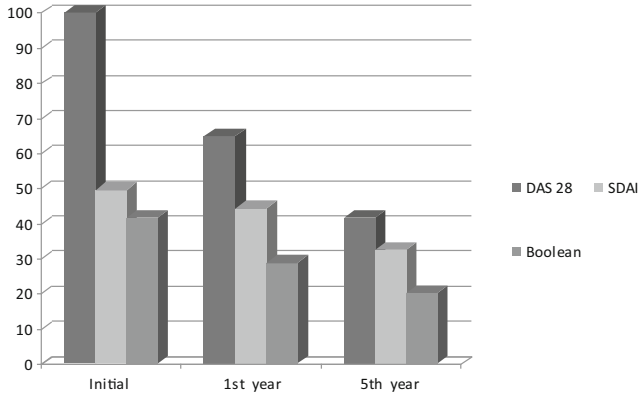

Fig. 1 The proportions of patients in remission according to DAS28, SDAI, and Boolean criteria at initial, first-year, and fifth-year visits

Lillegraven et al. reported that an increased number of visits in remission by any criteria were associated with reduced radiographic damage [45] and it was shown that sustained remission is associated with a halt of joint damage progression [5]. From this point of view, we examined the performance of DAS28, SDAI, and Boolean criteria in predicting sustainability of remission by comparing DAS28 remission visit counts of patients in three remission groups during the follow-up period. We found no significant difference but at the same time, the remission visit ratio of patients in SR was significantly higher than the N-SR group.

All of remission criteria evaluate disease activity at a single timepoint and are inadequate to satisfy the need for long-term follow-up of patients. None of these composite indices comprise all aspects of disease activity and a time perspective for assessing activity of RA as a chronic disease. Besides that, no uniform definition of sustained remission or frequency of assessments during the remission sustenance has been employed. The reported definition of remission duration varied from at least 6 months to 9–12 months in different studies. As the period in remission increases, the likelihood of patients experiencing flare after remission decreases [46, 47]. In our study, the remission rate at the fifth year determined by SDAI criteria was not different from the enrollment when the duration of remission defined as 6 and 12 months but Boolean criteria required sustenance of remission as long as 12 months to provide similar consistency. Studenic and his colleagues have shown that SDAI is more tolerant to isolated PtGA and CRP elevations than Boolean criteria because index-based remission criteria is a summative score and slight elevations of variables can be compensated for by others [12].

There are a number of limitations to our study. First of all, our study group has a small sample size and second, consists of patients with established RA. Schipper et al. reported that time to remission is the strongest predictor of sustained remission [31]. We did not have knowledge about the first remission period of our patients so it would not be possible to interpret our results in patients with early RA. The prospective follow-up of patients in an observational study design is the strength of our study despite these limitations.

In summary, we have shown that a low DAS28 score and functional disability assessed by HAQ and anti-CCP positivity are positive predictors of sustained remission and these results could guide physicians predicting patients with low/high relapse risk in clinical practice. To achieve sustained remission, patients with RA might be assessed with regard to symptoms of anxiety, depression, fibromyalgia, and fatigue because these non-inflammatory pain sources were more among patients in non-sustained remission group. Compared with the DAS28, the remission determined by Boolean and especially SDAI continued consistently in long term. Instead of 6 months, remission duration for ≥ 12 months would probably help us to predict SR independently from the chosen criteria; Boolean or SDAI.

Compliance with ethical standards

Written informed consent was obtained from all patients and the study was approved by the Marmara University School of Medicine Ethics Committee for Clinical and Laboratory Research (the approval number was 09.2012.0208).

Disclosures None.

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