

Effect of sustained intensive therapy with disease modifying anti-rheumatic drugs in rheumatoid arthritis: a 5-year real-world consecutive study

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Abstract

Background: Intensive therapy with disease modifying anti-rheumatic drugs (DMARDs) has been reported to improve the outcomes of rheumatoid arthritis (RA). However, real-world study on the effect of intensive therapy on RA sustained remission is still lacking. This study aimed to investigate the outcome of sustained intensive DMARD therapy (SUIT) for RA in a real-world 5-year consecutive cohort.

Methods: Based on a consecutive cohort of 610 out-patients with RA, remission of RA was assessed in 541 patients from 2012 to 2017, by dividing into SUIT, non-SUIT, and intermittent SUIT (Int-SUIT) groups. Changes in the disease activity scores were evaluated by 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR), 28-joint disease activity score based on C-reactive protein (DAS28-CRP), and clinical deep remission criteria (C-IDR). Cumulative remission rates between different groups were compared using Kaplan-Meier curves and predictive factors of sustained remission were identified by univariate and multivariate logistic regression analysis.

Results: The remission rates of the SUIT group decreased from 12.0% (65/541) to 5.6% (20/359) based on DAS28-ESR, from 14.0% (76/541) to 7.2% (26/359) based on DAS28-CRP, and from 8.5% (46/541) to 3.1% (11/359) based on C-IDR, respectively, with a gradually decreasing trend during the 5 years. The SUIT regimen led to a significantly higher cumulative remission rate than non-SUIT regimen based on DAS28-ESR (39.7% vs. 19.5%, $P = 0.001$), DAS28-CRP (42.0% vs. 19.6%, $P = 0.001$), and C-IDR (24.5% vs. 8.7%, $P = 0.001$). The cumulative remission rates of patients treated with SUIT regimen were significantly higher than those treated with Int-SUIT regimen based on DAS28-ESR (39.7% vs. 25.7%, $P = 0.043$) and C-IDR (24.5% vs. 14.2%, $P = 0.047$), but there was no significant difference between the two groups based on DAS28-CRP (42.0% vs. 27.4%, $P = 0.066$). Multivariate logistic regression analysis showed that the use of SUIT regimen was an independent favorable predictor according to different remission definitions (for DAS28-ESR: odds ratio [OR], 2.215, 95% confidence interval [CI]: 1.271–3.861, $P = 0.005$; for DAS28-CRP: OR, 1.520, 95% CI: 1.345–1.783, $P = 0.002$; for C-IDR: OR, 1.525, 95% CI: 1.314–1.875, $P = 0.013$).

Conclusion: Sustained intensive treatment of RA is an optimal strategy in daily practice and will lead to an increased remission rate.

Keywords: Rheumatoid arthritis; Remission; Sustained intensive therapy; Cohort study

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammatory synovitis and the subsequent destruction of articular cartilage and bone. Over the last few decades, a dramatic revolution on disease

remission has made the satisfactory outcome achievable with effective drugs and treatment strategies. Stringent control of disease activity lowers the risk of joint destruction, functional disability, and overall mortality in patients with RA.^[1] Intensive therapy involves the combination of synthetic, or biological disease modifying

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anti-rheumatic drugs (DMARDs), and steroids that is superior to routine step-up DMARD treatment and leads to improved outcomes in patients with RA.^[2] As treatment strategies continue to improve and remission becomes the target of treatment, rheumatologists are posed with challenging questions regarding sustained remission. Once remission has been achieved and stably maintained, should drugs be tapered or discontinued?

Suppression of disease activity for a prolonged period in RA is a hallmark that ideally implies the absence of any detectable swollen and tender joint, as well as any sign of systemic inflammation. Almost all clinical indices currently used to define disease remission allow residual inflammation, including Disease Activity Score 28 (DAS28), Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). Since DAS28 remission is afflicted with the potential of having swollen joints, it is related to damage progression.^[3] Active joints remained in SDAI and CDAI remission.^[4] Furthermore, the Boolean definition allows a maximum of one swollen and tender joint, which is closer to “deep” remission than the others.^[5] A more rigorous remission has been described by Wells *et al.*^[6] The criteria of Outcome Measures in Rheumatology (OMERACT) 7 are regarded as a more ambitious definition requiring a tender joint count of 0, a swollen joint count of 0, and an erythrocyte sedimentation rate (ESR) ≤ 10 mm/h, without C-reactive protein (CRP) included. Recently, Liu *et al.*^[7] described clinical deep remission (CliDR) as having no swollen or tender joint with a normal ESR and CRP level. Compared to the other remission definitions, CliDR is more stringent in evaluating the improvement and is easy to apply in practice.

It has been clearly shown that “tight control” is critical in improving the outcome of RA. However, rational regimens in practice need to be evaluated to provide clinical evidence in real world. In this study, we investigated the remission rate and predictive factors in a large cohort of patients with RA treated with sustained intensive DMARD therapy (SUIT), non-SUIT, and intermittent SUIT (Int-SUIT).

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and approved by the Institutional Research Ethics Committee of the Peking University People’s Hospital (No. 2018PHB006-01). Written informed consent was obtained from all patients.

Study population

This single-center daily practice cohort study was performed at the Peking University People’s Hospital between 2012 and 2017. Patients with active RA fulfilling the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/European League Against Rheumatism (EULAR) RA classification criteria were included in this study: (1) Age >18 years with at least three visits per year between January 2012 and December

2017; and (2) patients without other systemic inflammatory or connective tissue disease (CTD).

A total of 610 patients with active RA were selected from the medical records of 2012. During the follow-up period, seven patients were excluded due to uncertain diagnosis of RA, ten were excluded because they were diagnosed with other CTD, and the remaining 52 were excluded for missing data during follow-up. Finally, 541 patients were included in the cohort. During the 5-year follow-up, 207 (38.3%) patients were treated with SUIT, 152 (28.1%) with non-SUIT, and 182 (33.6%) patients with Int-SUIT. The flow diagram is presented in Figure 1.

Data collection

Clinical and laboratory data, including gender, age, smoking status, RA family history, RA disease duration, swollen joint count in 28 joints (SJC28), tender joint count in 28 joints (TJC28), deformed joint count in 28 joints (DJC28), ESR, CRP, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, extra-articular manifestations, and medical history, were collected from the medical database of Peking University People’s Hospital. The use of DMARDs, including methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, as well as glucocorticoids, was monitored throughout the study period. The data were obtained at each follow-up visit.

Definition of remission

RA remission was defined according to the following three criteria: 28-joint disease activity score based on ESR (DAS28-ESR) ≤ 2.6 ,^[8] 28-joint disease activity score based on CRP (DAS28-CRP) ≤ 2.6 ,^[8] and clinical deep remission (CliDR) criteria.^[7] No universally accepted approach was used to summarize the disease activity over multiple visits during follow-up. Each patient had only one value or mean value of the disease activity score per year that indicated his annual disease activity. Sustained remission is defined as maintaining remission at least 1 year.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 23.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were described as counts (percentages) and continuous variables were expressed as mean \pm standard deviation or median (Q_1 , Q_3). The demographics and clinical characteristics between the groups were compared using Kruskal-Wallis *H* test for continuous variables with skewed distribution, one-way analysis of variance test for continuous variables with normal distribution and Chi-squared or Fisher exact test for categorical variables. Kaplan-Meier survival curves and log-rank test were applied to analyze the differences between groups in accumulative percentages of remission. Independent predictor identification was performed by forward stepwise multivariate logistic regression analysis. Variables with a *P*-value <0.10 in univariate regression analysis were retained for the multivariate model. A two-tailed *P*-value <0.05 was considered as statistically significant.

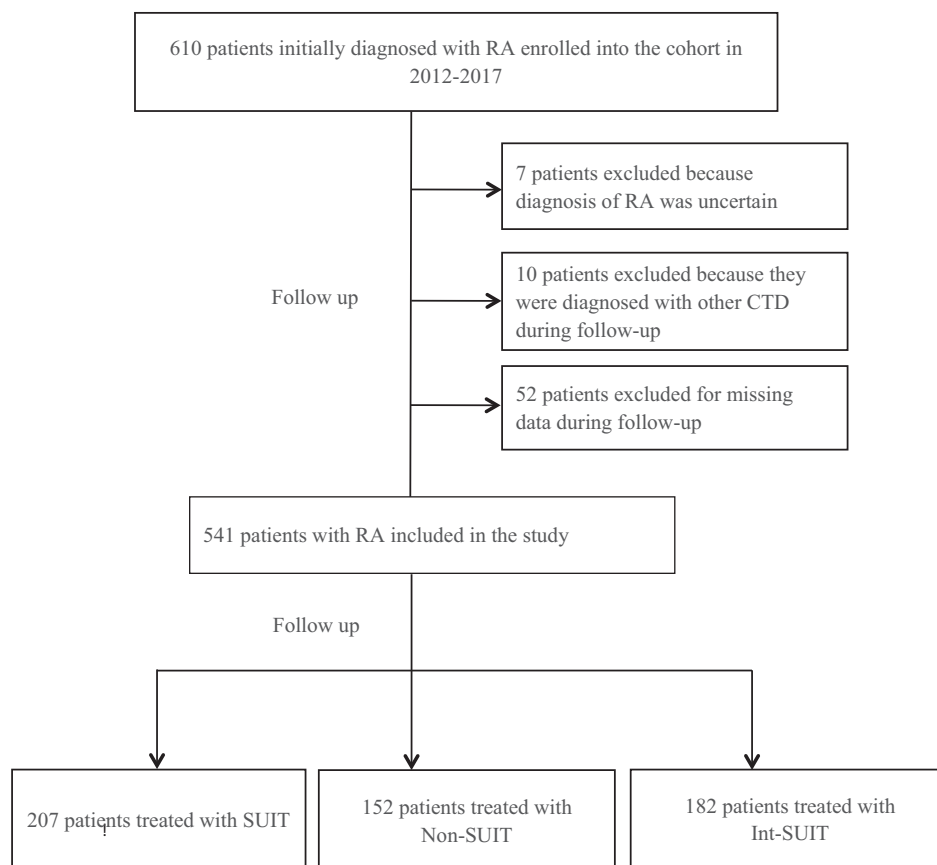


Figure 1: Flow diagram of the selection of the participants. RA: Rheumatoid arthritis; CTD: Connective tissue disease; SUIIT: Sustained intensive therapy with disease modifying anti-rheumatic drugs; Int-SUIIT: Intermittent SUIIT.

Results

Baseline characteristics of patients with RA

Among the 541 patients with RA, 457 (84.5%) were females with the mean age of 56.9 ± 12.7 years, and the mean disease duration was 10.7 ± 9.2 years. The median counts of tender, swollen, and deformed joints were 9, 7, and 2, respectively. The median levels of ESR and CRP were 42.7 mm/h and 17.9 mg/L, respectively. Positive RF and anti-CCP antibodies were observed in 385 (71.2%) and 515 (95.2%) patients, respectively. Interestingly, osteoarthritis (116/541, 21.4%) was the most common complication. Interstitial lung disease (47/541, 8.7%) and secondary Sjögren syndrome (41/541, 7.6%) were the most common extra-articular manifestations. The usage rate of conventional synthetic DMARDs was 93.0% (503/541) with methotrexate (217/541, 40.1%), leflunomide (307/541, 56.7%), and hydroxychloroquine (175/541, 32.3%). In the initial treatment, 29.8% (161/541) of the patients received glucocorticoids, and 7.0% (38/541) used biological DMARDs. We also compared the baseline characteristics among SUIIT, Int-SUIIT, and non-SUIIT groups. No significant differences were detected in age, gender, anti-CCP antibodies, CRP, ESR, TJC28, SJC28, and DJC28 ($P > 0.05$). However, there were significant differences in RF, RA family history, and smoking among the three groups ($P < 0.05$) [Table 1].

Trends of sustained remission

A total of 12.0% (65/541) of patients sustained at least 1-year DAS28-ESR remission in the SUIIT group, 8.5% (46/541) in the Int-SUIIT group, and 3.5% (19/541) in the non-SUIIT group. In the three groups, the remission rates decreased gradually with time. Only 5.6% (20/359) of patients maintained remission in consecutive 5 years in the SUIIT group, 0.8% (3/359) in the Int-SUIIT and 0.3% (1/359) in the non-SUIIT groups [Figure 2A]. Consequently, a higher percentage of patients sustained remission in the SUIIT group as compared to that in the non-SUIIT and Int-SUIIT groups. The same trend was observed when assessed by DAS28-CRP criteria. The remission rates of patients treated with SUIIT regimens decreased from 14.0% (76/541) to 7.2% (26/359) during the 5 years [Figure 2B]. The remission trend analyzed with CliDR criteria revealed that the remission rate decreased from 8.5% (46/541) to 3.1% (11/359) in the SUIIT group during the 5 years. However, only 4.8% (26/541) of the patients in the non-SUIIT group and 2.6% (14/541) in the Int-SUIIT group achieved 1-year sustained remission. Surprisingly, patients with sustained CliDR remission >3 years were rare, and the remission rates were nearly 0 in the non-SUIIT and Int-SUIIT groups [Figure 2C].

RA cumulative remission rates in 5 years

As shown in Figure 3, significantly different cumulative remission rates were found between the three treatment groups

Table 1: Baseline characteristics of patients with RA treated with different regimens.

Characteristics	Total (n = 541)	SUIT (n = 207)	Non-SUIT (n = 152)	Int-SUIT (n = 182)	Statistics	P
Age (years)	56.9 ± 12.7	53.6 ± 11.6	60.8 ± 12.5	57.2 ± 13.2	2.796*	0.062
Female	457 (84.5)	180 (87.0)	123 (80.9)	154 (84.6)	2.438†	0.295
Smoking	40 (7.4)	12 (5.8)	7 (4.6)	21 (11.5)	7.063†	0.028
RA family history	28 (5.2)	8 (3.9)	4 (2.6)	16 (8.8)	7.577†	0.023
CRP (mg/L)	17.9 (8.6, 27.2)	16.3 (8.1, 25.7)	13.4 (6.3, 21.1)	19.5 (8.8, 29.3)	0.603‡	0.547
ESR (mm/h)	42.7 (20.1, 64.8)	42.5 (20.2, 62.1)	41.4 (18.6, 63.8)	44.4 (20.2, 67.4)	0.638‡	0.529
TJC28	9 (4, 15)	8 (4, 14)	9 (4, 15)	9 (4, 15)	0.151‡	0.859
SJC28	7 (4, 13)	7 (4, 13)	6 (3, 10)	7 (4, 11)	0.924‡	0.398
DJC28	2 (1, 3)	2 (1, 3)	1 (0, 2)	2 (1, 3)	2.645‡	0.072
RF positivity	385 (71.2)	159 (76.8)	94 (61.8)	132 (72.5)	9.819†	0.007
Anti-CCP positivity	515 (95.2)	201 (97.1)	143 (94.1)	171 (94.0)	0.273†	0.872

Data are presented as mean ± standard deviation, median (Q₁, Q₃), or n (%). RF positivity refers to RF values >20 mg/dL. * F value. † χ^2 value. ‡ H value. RA: Rheumatoid arthritis; SUIT: Sustained intensive therapy with disease modifying anti-rheumatic drugs; Int-SUIT: Intermittent SUIT; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TJC28: Tender joint count in 28 joints; SJC28: Swollen joint count in 28 joints; DJC28: Deformed joint count in 28 joints; RF: Rheumatoid factor; CCP: Cyclic citrullinated peptide.

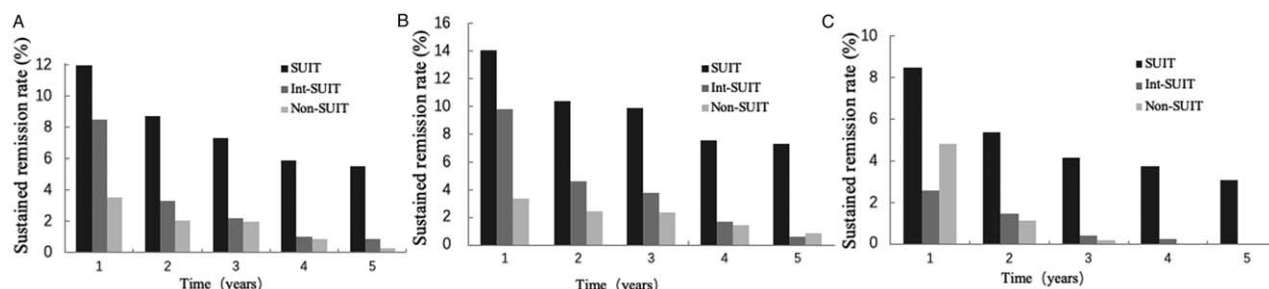


Figure 2: Sustained remission rates in patients with RA treated with different regimens based on (A) DAS28-ESR, (B) DAS28-CRP, and (C) CliDR criteria. RA: Rheumatoid arthritis; DAS28-ESR: 28-Joint disease activity score based on erythrocyte sedimentation rate; DAS28-CRP: 28-Joint disease activity score based on C-reactive protein; CliDR: Clinical deep remission; SUIT: Sustained intensive therapy with disease modifying anti-rheumatic drugs; Int-SUIT: Intermittent SUIT.

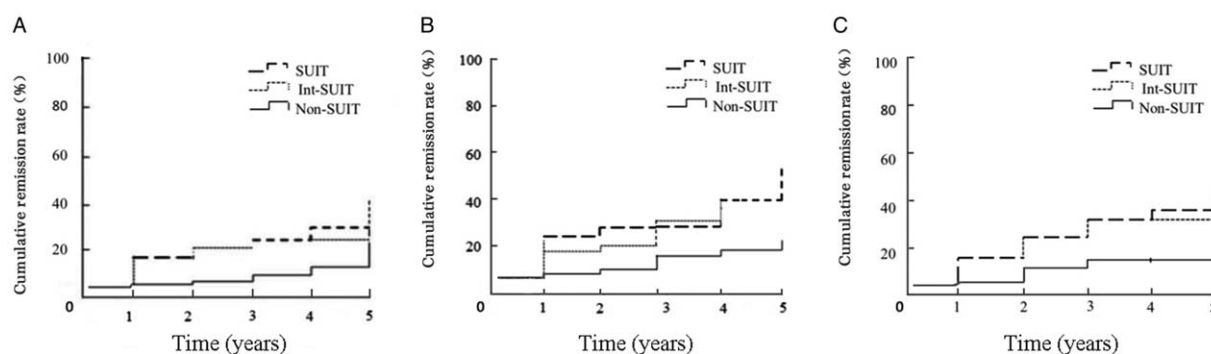


Figure 3: Kaplan-Meier analysis of cumulative sustained remission rates in patients with RA treated with different regimens based on (A) DAS28-ESR, (B) DAS28-CRP, and (C) CliDR criteria. RA: Rheumatoid arthritis; DAS28-ESR: 28-Joint disease activity score based on erythrocyte sedimentation rate; DAS28-CRP: 28-Joint disease activity score based on C-reactive protein; CliDR: Clinical deep remission; SUIT: Sustained intensive therapy with disease modifying anti-rheumatic drugs; Int-SUIT: Intermittent SUIT.

based on DAS28-ESR ($P = 0.002$), DAS28-CRP ($P < 0.001$), and CliDR ($P = 0.001$) throughout the 5-year period. Compared to those with non-SUIT and Int-SUIT regimens, patients treated with SUIT regimen had a significantly higher cumulative remission rate when assessed by DAS28-ESR (39.7% vs. 19.5%, $P = 0.001$; 39.7% vs. 25.7%, $P = 0.043$, respectively) and CliDR (24.5% vs. 8.7%, $P = 0.001$; 24.5% vs. 14.2%, $P = 0.047$, respectively). Based on DAS28-CRP

regimen was significantly higher than that with non-SUIT regimen (42.0% vs. 19.6%, $P = 0.001$), although no significant difference was detected between patients with SUIT and Int-SUIT regimen (42.0% vs. 27.4%, $P = 0.066$).

Predictors of sustained remission in patients with RA

The univariate logistic analysis showed that age (odds ratio [OR], 0.959, 95% confidence interval [CI]: 0.942–0.975,

Table 2: Univariate and multivariate logistic regression analysis of predictors for sustained remission of RA (N=541).

Items	Sustained remission	No remission	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P	OR (95% CI)	P
DAS28-ESR remission						
Achieving remission	130 (24.0)	411 (76.0)				
Age (years)	51.0 ± 14.7	58.7 ± 11.4	0.959 (0.942–0.975)	<0.001	0.962 (0.944–0.980)	<0.001
Female	111 (85.4)	346 (84.2)	0.981 (0.488–1.974)	0.957		
Smoking	4 (3.1)	23 (5.6)	0.820 (0.145–4.648)	0.171		
Anti-CCP positivity	118 (90.8)	396 (96.4)	0.998 (0.994–1.002)	0.270		
RF positivity	103 (79.2)	344 (83.7)	1.000 (0.999–1.000)	0.607		
ESR (mm/1 h)	36.2 (17.1, 54.1)	44.9 (22.0, 67.1)	0.988 (0.980–0.997)	0.012	0.987 (0.957–0.997)	0.015
CRP (mg/L)	15.0 (7.3, 22.6)	18.8 (9.0, 27.2)	1.001 (0.989–1.012)	0.931		
SJC28	5 (2, 9)	7 (4, 13)	0.964 (0.930–0.996)	0.030	0.952 (0.917–0.989)	0.011
TJC28	7 (4, 13)	9 (4, 15)	1.005 (0.971–1.041)	0.764		
SUIT regimen	65 (50.0)	142 (34.5)	1.630 (1.410–1.960)	0.033	2.215 (1.271–3.861)	0.005
DAS28-CRP remission						
Achieving remission	147 (27.2)	394 (72.8)				
Age (year)	53.8 ± 13.6	58.0 ± 12.2	0.982 (0.966–0.998)	0.026	0.983 (0.967–0.999)	0.043
Female	133 (90.5)	324 (82.2)	0.522 (0.254–1.074)	0.077	0.911 (0.524–1.586)	0.742
Smoking	2 (1.4)	25 (6.3)	0.566 (0.067–4.786)	0.505		
Anti-CCP positivity	137 (93.2)	377 (95.7)	1.001 (0.997–1.004)	0.768		
RF positivity	123 (83.7)	324 (82.2)	1.000 (1.000–1.001)	0.161		
ESR (mm/1 h)	40.3 (20.1, 60.9)	43.8 (21.1, 65.9)	0.999 (0.989–1.009)	0.857		
CRP (mg/L)	14.4 (7.1, 21.8)	19.2 (9.6, 28.9)	0.996 (0.984–1.007)	0.486		
SJC28	5 (3, 9)	7 (4, 13)	0.980 (0.944–1.018)	0.304		
TJC28	7 (4, 13)	10 (5, 15)	0.950 (0.926–0.981)	0.001	0.997 (0.961–1.034)	0.865
SUIT regimen	76 (51.7)	131 (33.2)	1.520 (1.345–1.783)	0.002	1.520 (1.345–1.783)	0.002
CliDR remission						
Achieving remission	86 (15.9)	455 (84.1)				
Age (years)	50.2 ± 13.6	58.1 ± 12.2	0.961 (0.942–0.981)	<0.001	0.967 (0.948–0.986)	<0.001
Female	77 (89.5)	380 (83.5)	0.642 (0.257–1.602)	0.342		
Smoking	2 (2.3)	25 (5.5)	1.396 (0.108–1.799)	0.076	1.867 (0.634–1.502)	0.257
Anti-CCP positivity	81 (94.2)	433 (95.2)	1.002 (0.998–1.006)	0.335		
RF positivity	66 (76.7)	381 (83.7)	1.000 (0.997–1.000)	0.611		
ESR (mm/1 h)	34.2 (17.4, 51.3)	44.5 (22.1, 66.5)	0.987 (0.974–0.999)	0.038	1.012 (0.999–1.026)	0.079
CRP (mg/L)	11.0 (6.0, 17.1)	19.2 (9.3, 28.6)	0.990 (0.973–1.008)	0.276		
SJC28	5 (3, 9)	7 (4, 13)	0.947 (0.904–0.992)	0.022	0.986 (0.943–1.031)	0.542
TJC28	7 (4, 13)	9 (4, 15)	1.009 (0.967–1.054)	0.673		
SUIT regimen	46 (53.5)	161 (35.4)	1.525 (1.314–1.875)	0.014	1.525 (1.314–1.875)	0.013

Data are presented as mean ± standard deviation, median (Q₁, Q₃), or *n* (%). RF positivity refers to RF values >20 mg/dL. RA: Rheumatoid arthritis; OR: Odds ratio; CI: Confidence interval; DAS28-ESR: 28-joint disease activity score based on erythrocyte sedimentation rate; CCP: Cyclic citrullinated peptide; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; SJC28: Swollen joint count in 28 joints; TJC28: Tender joint count in 28 joints; RF: Rheumatoid factor; SUIT: Sustained intensive therapy with disease modifying anti-rheumatic drugs; DAS28-CRP: 28-Joint disease activity score based on C-reactive protein; CliDR: Clinical deep remission.

$P < 0.001$), ESR (OR, 0.988, 95% CI: 0.980–0.997, $P = 0.012$), SJC28 (OR, 0.964, 95% CI: 0.930–0.996, $P = 0.030$), and the use of SUIT regimen (OR, 1.630, 95% CI: 1.410–1.960, $P = 0.033$) were significantly associated with sustained DAS28-ESR remission. Age (OR, 0.982, 95% CI: 0.966–0.998, $P = 0.026$), TJC28 (OR, 0.950, 95% CI: 0.926–0.981, $P = 0.001$), and the use of SUIT regimen (OR, 1.520, 95% CI: 1.345–1.783, $P = 0.002$) were significantly associated with DAS28-CRP remission. Data also showed that age (OR, 0.961, 95% CI: 0.942–0.981, $P < 0.001$), ESR (OR, 0.987, 95% CI: 0.974–0.999, $P = 0.038$), SJC28 (OR, 0.947, 95% CI: 0.904–0.992, $P = 0.022$), and the use of SUIT regimen (OR, 1.525, 95% CI: 1.314–1.875, $P = 0.014$) were

significantly associated with sustained remission based on CliDR [Table 2].

Multivariate analysis revealed that young age and the use of SUIT regimen were independent favorable predictors of sustained DAS28-ESR remission (OR, 0.962, 95% CI: 0.944–0.980, $P < 0.001$; OR, 2.215, 95% CI: 1.271–3.861, $P = 0.005$, respectively), as well as sustained DAS28-CRP (OR, 0.983, 95% CI: 0.967–0.999, $P = 0.043$; OR, 1.520, 95% CI: 1.345–1.783, $P = 0.002$, respectively) and CliDR remission (OR, 0.967, 95% CI: 0.948–0.986, $P < 0.001$; OR, 1.525, 95% CI: 1.314–1.875, $P = 0.013$, respectively) for at least 1 year. ESR and SJC28 were found to be independent negative predictors only according to DAS28-

ESR (OR, 0.987, 95% CI: 0.957–0.997, $P=0.015$; OR, 0.952, 95% CI: 0.917–0.989, $P=0.011$, respectively) [Table 2].

Discussion

Remission is a key treatment goal and an increasingly achievable outcome in patients with RA. Achieving remission with DMARD treatment is recommended by several management guidelines.^[9,10] Sustained remission is the preferred treatment target in RA as patients in sustained remission show less joint damage progression than those in remission at a single time point.

The current study investigated the prevalence of sustained remission in patients with RA treated by SUI. It was shown that the sustained remission rate of patients treated with SUI regimen was significantly higher than that in patients with usual care (non-SUI and Int-SUI groups), although rare patients maintained remission during the 5-year follow-up. In this study, similar trends based on different criteria suggested that a larger number of patients with SUI regimen sustained remission than those with non-SUI and Int-SUI regimens. The more stringent the disease is controlled, the more patients can achieve sustained remission.

Several studies suggested the advantages of intensive strategy in RA treatment. As shown in the tight control for rheumatoid arthritis (TICORA) study,^[11] intensive treatment substantially improved the disease activity of patients with RA. In a study conducted in China, prolonged intensive DMARD therapy was found to induce a high rate of good EULAR response.^[12] The current study suggested further that SUI might be an effective strategy to maintain sustained remission.

However, in clinical practice, patients, especially elderly and those with comorbidities, are always reluctant to sustain tight control due to fear of adverse reactions. Older age might be the main barrier to implement the SUI strategy. Consequently, such patients might require tapered DMARDs rapidly after reaching the treatment goal, leading to relapse and poor prognosis. EULAR recommendation suggested that if a patient is in persistent remission, tapering the conventional DMARDs could be considered. However, the duration of persistence is yet to be deduced, thereby necessitating additional evidence for consensus.

Identifying the type of patients that would easily obtain the treatment target and maintain remission after tapering DMARDs is crucial for developing personalized and stratified treatment strategies in RA. In a previous study, male gender, high education level, and low baseline disease activity were suggested to be predictors of remission, while initial use of corticosteroids was negatively associated with remission.^[13] Fewer studies have investigated the association between the use of SUI regimen and sustained remission. In this study, the results showed that treatment with SUI regimen was an independent predictor assessed by different remission definitions, suggesting “tight control” as a “remission-inducing” strategy in patients with RA. In addition, younger age and low ESR predicted

the sustained remission as described previously.^[14] Presently, a variety of validated tools, such as DAS28, CDAI, SDAI, and Boolean definition, are available to assess the remission of patients with RA. However, there is no consensus on the optimal approach. Most of the patients with RA in remission, based on the current definitions, showed signs of residual inflammation.^[15,16] In the current study, we assessed the sustained remission rates by CliDR. It is a more rigorous criteria and the sustained remission according to it is quite low. Further studies are still necessary to evaluate this novel remission definition. In this study, SDAI and Boolean remission were not analyzed due to the lack of evaluation of patient global visual analogue scale. Other limitations include absence of radiographic evaluation and laboratory parameters.

In conclusion, the current study suggested that RA remission was not common in the real world. Thus, sustained intensive treatment of RA is an optimal strategy, and will improve remission and outcome of the disease in clinical practice.

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Conflicts of interest

None.

References

- van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B, Boers M, *et al.* Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. *Arthritis Care Res (Hoboken)* 2010;62:108–117. doi: 10.1002/acr.20021.
- O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, *et al.* Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013;369:307–318. doi: 10.1056/NEJMoa1303006.
- Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;52:2625–2636. doi: 10.1002/art.21235.
- Smolen JS, Aletaha D. Scores for all seasons: SDAI and CDAI. *Clin Exp Rheumatol* 2014;32 (Suppl 85):S75–S79.
- Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, *et al.* American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;63:573–586. doi: 10.1002/art.30129.
- Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, *et al.* Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005;32:2016–2024.
- Liu JJ, Li R, Gan YZ, Zhang RJ, Li J, Cai YM, *et al.* Clinical deep remission and related factors in a large cohort of patients with rheumatoid arthritis. *Chin Med J* 2019;132:1009–1014. doi: 10.1097/CM9.0000000000000227.
- Prevo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–48. doi: 10.1002/art.1780380107.
- Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, *et al.* EULAR recommendations for the management of

- rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–977. doi: 10.1136/annrheumdis-2016-210715.
10. Singh JA, Saag KG, Bridges SJ Jr, Akl EA, Bannuru RR, Sullivan MC, *et al.* 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26. doi: 10.1002/art.39480.
 11. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263–269. doi: 10.1016/S0140-6736(04)16676-2.
 12. Li R, Zhao JX, Su Y, He J, Chen LN, Gu F, *et al.* High remission and low relapse with prolonged intensive DMARD therapy in rheumatoid arthritis (PRINT): A multicenter randomized clinical trial. *Medicine (Baltimore)* 2016;95:e3968. doi: 10.1097/MD.0000000000003968.
 13. Yu C, Jin S, Wang Y, Jiang N, Wu C, Wang Q, *et al.* Remission rate and predictors of remission in patients with rheumatoid arthritis under treat-to-target strategy in real-world studies: a systematic review and meta-analysis. *Clin Rheumatol* 2019;38:727–738. doi: 10.1007/s10067-018-4340-7.
 14. Einarsson JT, Willim M, Ernestam S, Saxne T, Geborek P, Kapetanovic MC. Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a Nationwide Study in Sweden. *Rheumatology (Oxford)* 2019;58:227–236. doi: 10.1093/rheumatology/key054.
 15. Mäkinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis. *Ann Rheum Dis* 2005;64:1410–1413. doi: 10.1136/ard.2005.037333.
 16. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R, *et al.* Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. *Ann Rheum Dis* 2011;70:792–798. doi: 10.1136/ard.2010.134445.
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