Clinical deep remission and related factors in a large cohort of patients with rheumatoid arthritis

Jia-Jia Liu[1,2], Ru Li[1,2], Yu-Zhou Gan[1,2], Rui-Jun Zhang[1,2], Jing Li[1,2], Yue-Ming Cai[3], Jin-Xia Zhao[4], Hua Liao[5], Jing Xu[6], Lian-Jie Shi[6], Ji Li[6], Sheng-Guang Li[6], Xiao-Lin Sun[1,2], Jing He[1,2], Xu Liu[1,2], Hua Ye[1,2], Zhan-Guo Li[1,2,7,8]

[1]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing 100044, China;
[2]Beijing Key Laboratory for Rheumatism Mechanism and Immune Diagnosis (BZ0135), Beijing 100044, China;
[3]Department of Rheumatology and Immunology, Peking University Shenzhen Hospital, Shenzhen, Guangdong 518035, China;
[4]Department of Rheumatology and Immunology, Peking University Third Hospital, Beijing 100191, China;
[5]Department of Rheumatology and Immunology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100129, China;
[6]Department of Rheumatology and Immunology, Peking University International Hospital, Beijing 102206, China;
[7]Peking-Tsinghua Center for Life Sciences, Beijing 100044, China;
[8]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100044, China.

Abstract

Background: Clinical remission is the treatment target in rheumatoid arthritis (RA). This study aimed to investigate clinical remission and related factors in a large cohort of patients with RA.

Methods: This study composed of 342 patients with RA. Data were collected by face-to-face interview of 1049 patients with RA who visited the Department of Rheumatology of three teaching hospitals from September 2015 to May 2016. The patients with RA were clinically assessed by rheumatologists and a four-page questionnaire was completed on site. Subsequently, patients fulfilled remission criteria were further analyzed. The practicability of different definitions of remission of RA was rated by a panel of rheumatologists. Sustained intensive disease modifying anti-rheumatic drug (DMARD) treatment was defined as a combination treatment with two or more DMARDs for at least 6 months.

Results: In this cohort of 342 patients with RA, the proportions of patients achieving remission were 38.0%, 29.5%, 24.9%, 21.1%, 19.0%, 18.1%, and 17.0%, based on criteria of disease activity score in 28 joints (DAS28) using CRP (DAS28-CRP), DAS28 using ESR (DAS28-ESR), routine assessment of patient index data 3 (RAPID-3), Boolean, simplified disease activity index (SDAI), clinical disease activity index, and the newly described clinical deep remission (CliDR), respectively. Boolean and CliDR are the best in practicability scored by rheumatologists (7.5 and 8.0, respectively). Compared with the non-sustained intensive group, sustained intensive treatment with DMARDs yielded higher remission rates of 25.6%, 23.8%, and 21.3% in patients with RA based on Boolean ($\chi^2 = 3.937$, $P = 0.047$), SDAI ($\chi^2 = 4.666$, $P = 0.031$), and CliDR criteria ($\chi^2 = 4.297$, $P = 0.038$). The most commonly prescribed conventional synthesized DMARDs (csDMARDs) in patients with RA was leflunomide, followed by methotrexate, and hydroxychloroquine. Compared with the non-remission group, patients achieving remission had a longer median duration of DMARDs (45.0 [22.8–72.3] months, $Z = -2.295$, $P = 0.022$).

Conclusions: The findings in this study indicated that clinical deep remission is achievable in patients with RA. Sustained intensive DMARD treatment is needed to achieve a better outcome in RA.

Keywords: Rheumatoid arthritis; Remission; Sustained; Intensive; Disease modifying anti-rheumatic drug

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease leading to joint destruction and disability.[1] Health-related quality of life is impaired due to pain, fatigue, and loss of physical function in patients with RA experience.[2] During the last two decades, earlier initiation of disease modifying anti-rheumatic drugs (DMARDs), especially the use of biologic DMARDs (bDMARDs), has revolutionized the treatment of RA, resulting in achievement of clinical remission or low disease activity in an increasing proportion of patients.[3] In patients with new-onset RA, remission is realistic. Even sustained and drug-free remission is proven to be feasible.[4]

Several definitions are available to evaluate the disease activity of RA, such as Disease Activity Score in 28 joints

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000227

Correspondence to: Dr. Zhan-Guo Li, Department of Rheumatology and Immunology, Peking University People's Hospital, No. 11, Xizhimen South Street, Beijing 100044, China
E-Mail: zgli99@aliyun.com

Chinese Medical Journal 2019;132(9)

Received: 03-01-2019 **Edited by:** Ning-Ning Wang

(DAS28) using ESR (DAS28-ESR), DAS28 using CRP (DAS28-CRP), Routine Assessment of Patient Index Data 3 (RAPID-3), simplified disease activity index (SDAI), clinical disease activity index (CDAI), and Boolean. However, most of patients with RA in remission based on the current definitions show signs of residual inflammation.[5,6] Moreover, among patients with RA who had already achieved and even maintained remission for 2 years, nearly half of them relapsed and 19% to 30% experienced radiologic progression during follow-up.[7,8] In addition, the patient global assessment (PtGA) is a limiting factor for remission assessment due to its subjectivity.[9-11] Many patients without visible inflammation did not reach remission because of PtGA.[12] Therefore, a more feasible definition of remission is needed to evaluate disease status and to guide treatment in daily practice.

It has been shown that improved outcome of RA is related to prolonged and deep remission.[13-15] In the COBRA trial, an initial 6-month cycle of intensive combination treatment that includes high-dose corticosteroids resulted in sustained suppression of the rate of radiologic progression in patients with early RA.[13] Similarly, prolonged intensive DMARDs therapy (PRINT) consisting of methotrexate (MTX), leflunomide (LEF), and hydroxychloroquine (HCQ) also led to a high remission rate and a low risk of flare after DMARD tapering.[14]

In this study, we investigated the prevalence of remission based on different criteria and effect of sustained intensive treatment on clinical remission in a large cohort of patients with RA.

Methods

Ethical approval

The study was approved by the institutional review board of the Peking University People's Hospital. All patients provided written informed consents to participate in the study.

This large scale, observational, multicenter, cross-sectional retrospective study included patients with RA according to 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) criteria and 1987 RA criteria of the ACR.[16,17] DAS28-ESR, DAS28-CRP, RAPID-3, SDAI, CDAI, and Boolean were used as described elsewhere,[18-22] and clinical deep remission (CliDR) was defined as having no swollen or tender joint with a normal ESR and CRP level. Sustained intensive DMARD treatment was defined as a combination treatment with two or more DMARDs for at least 6 months. BioDMARDs were considered as DMARDs in the present study, but not glucocorticoid.

Study population

Patients were recruited among the outpatients and inpatients who visited the rheumatology department of Peking University People's Hospital, Peking University Third Hospital, and Peking University International Hospital between September 2015 and May 2016. Patients with other autoimmune disease or cancer were excluded in the current study. Ultimately, 342 patients were included in the study.

Clinical evaluation

Rheumatologists completed a three-page form on each patient: (1) information on all previous and present DMARDs taken, their adverse events, and reasons for discontinuation; and (2) results of a 28-joint count including a swollen joint count (SJC) and tender joint count (TJC), as well as a count of joints with limited motion or deformity. The review included the physician global assessment (PhGA) of disease activity on a visual analog scale (VAS) of 0 to 10 score, with 10 denoting the maximum fatigue/pain/disease activity and 0 denoting the minimum. The review also included findings of laboratory tests, that is, ESR, CRP level, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) status. The practicability of different definitions was rated by 42 rheumatologists.

Patient questionnaires

Patients completed a four-page expanded self-report questionnaire, including the multidimensional health assessment questionnaire (MDHAQ) to assess functional capacity in activities of daily living. Pain, fatigue, and PtGA were assessed on a VAS of 0 to 10 score. Information on lifestyle choices such as smoking was collected.

Statistical analysis

Statistical analysis was performed with SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA). Values of $P \leq 0.05$ were considered statistically significant. The distributions of continuous variables were examined. Data were expressed as mean ± standard deviation (SD) for normally distributed continuous variables and median (interquartile range [IQR]) for skewed continuous variables. Absolute and relative frequencies were reported for categorical variables. Remission rates were calculated based on each of the seven definitions.

Comparisons of the demographics, clinical characteristics, and treatments between two groups were performed using Student *t* tests for normally distributed continuous variables, Mann-Whitney *U* tests for skewed continuous variables, and the Chi-squared tests for categorical variables.

Results

Demographic characteristics of patients with RA

Among the 342 patients with RA, 254 patients (74.3%) were females. The mean age was 54.5 ± 13.6 years, with a median disease duration of 70.5 months (IQR: 32.0–156.0 months) [Table 1]. Nearly half (45.3%) of the included patients were smokers of which 56.8% were exposed to second-hand smoking and the others were previous or current smokers. Twenty of 342 patients (5.9%) had a positive family history of RA. Anti-CCP was positive in 76.0% of the cohort, and RF was 64.0%. The median MDHAQ score was 0.1 (IQR: 0–0.3).

Table 1: Characteristics of enrolled rheumatoid arthritis patients.

Characteristics	Values
Patients, *n*	342
Age (years), mean ± SD	54.5 ± 13.6
Female, *n* (%)	254 (74.3)
Disease duration (months), median (IQR)	70.5 (32.0–156.0)
Smoking,* *n* (%)	155 (45.3)
RA positive family history, *n* (%)	20 (5.9)
Disease activity characteristics,	
Median (IQR)	
TJC	2 (0–5)
SJC	1 (0–4)
ESR (mm/h)	17.0 (10.0–30.3)
CRP (mg/dL)	3.8 (1.9–10.7)
RF positive, *n* (%)	219 (64.0)
Anti-CCP positive, *n* (%)	260 (76.0)
Pain,† median (IQR)	2.5 (1.0–5.0)
PtGA,† median (IQR)	3.0 (1.0–5.0)
PhGA,† median (IQR)	2.0 (1.0–4.0)
MDHAQ score,‡ median (IQR)	0.1 (0–0.3)
Treatment, *n* (%)	
Synthetic DMARDs	313 (91.5)
MTX	204 (59.7)
LEF	228 (66.7)
HCQ	160 (46.8)
SSZ	89 (26.0)
Iguratimod	23 (6.7)
bDMARDs	50 (14.6)
Glucocorticoids	95 (27.8)

* Second hand smoking is included in smoking. †0–10 scores. ‡0–3 scores. Anti-CCP: Anti-cyclic citrullinated peptide; bDMARDs: Biologic DMARDs; CRP: C-reactive protein; DMARD: Disease modifying anti-rheumatic drug; ESR: Erythrocyte sedimentation rate; HCQ: Hydroxychloroquine; IQR: Interquartile range; LEF: Leflunomide; MDHAQ: Multidimensional health assessment questionnaire; MTX: Methotrexate; PhGA: Physician observer global assessment; PtGA: Patient global assessment; RF: Rheumatoid factors; SD: Standard deviation; SJC: Swollen joint count; SSZ: Sulfasalazine; TJC: Tender joint count.

Remission rates based on different definitions

In this cohort of 342 patients with RA, remission rates differed based on various criteria [Table 2]. The proportions of patients achieving remission were the highest on the DAS28-CRP (38.0%), followed by DAS28-ESR (29.5%), RAPID-3 (24.9%), Boolean (21.1%), SDAI (19.0%), CDAI (18.1%), and CliDR (17.0%). Compared to the other criteria, Boolean, SDAI, CDAI, and CliDR were more stringent.

To investigate the practicability of these criteria, 42 rheumatologists from several hospitals evaluated the various remission definitions on a scale of 0 to 10 score, with 10 denoting the maximum practicability and 0 the minimum. As shown in Table 3, the CliDR was found to be the most feasible criteria to use in daily practice.

Effect of treatment on remission

The effects of treatment on remission were analyzed [Table 4]. Unlike non-remission patients, all of the

Table 2: Remission rates of 342 patients based on different definitions, *n* (%).

Definitions	Remission rates
DAS28-CRP	130 (38.0)
DAS28-ESR	101 (29.5)
Boolean	72 (21.1)
RAPID-3	85 (24.9)
SDAI	65 (19.0)
CDAI	62 (18.1)
CliDR	58 (17.0)

CDAI: Clinical disease activity index; CliDR: Clinical deep remission; DAS28-CRP: Disease activity score in 28 joints using CRP; DAS28-ESR: Disease activity score in 28 joints using ESR; RAPID-3: Routine assessment of patient index data 3; SDAI: Simplified disease activity index.

remission patients were taking DMARDs ($\chi^2 = 5.222$, $P = 0.022$). The most often prescription of conventional synthesized DMARDs (csDMARDs) in patients with RA was LEF, followed by MTX, HCQ, SSZ, and iguratimod. None of these csDMARDs was more frequently used in the remission group. However, compared to the non-remission group, more patients (75.9%) achieved remission under combination therapy during this investigation ($\chi^2 = 4.326$, $P = 0.038$). The median duration of therapy was 45.0 months (IQR: 22.8–72.3 months) in patients achieving CliDR, which was statistical significantly longer than that in the non-remission patients (median duration [IQR]: 30 [9.0–72.8] months, $Z = -2.295$, $P = 0.022$). These data indicated that the treatment duration and combination therapy was strictly associated with remission.

Sustained intensive DMARD treatment and remission

To further identify the effect of treatment duration and combination therapy on disease remission in real-world data, we divided the patients into a sustained intensive DMARD treatment group and a non-sustained intensive DMARD treatment group on the basis of treatment during the last 6 months. About 164 (48.0%) patients with sustained intensive DMARD treatment achieved higher remission rates based on the seven criteria, particularly according to Boolean (25.6%, $\chi^2 = 3.937$, $P = 0.047$), SDAI (23.8%, $\chi^2 = 4.666$, $P = 0.031$), and CliDR (21.3%, $\chi^2 = 4.297$, $P = 0.038$) [Figure 1A].

The disease and therapy durations in patients with sustained intensive DMARD treatment were 124.8 ± 106.1 and 66.7 ± 53.7 months, which were longer than those with non-intensive therapy (93.0 ± 101.0 and 38.6 ± 51.9 months; $t = 2.840$, $P = 0.005$ for disease duration and $t = 4.922$, $P < 0.001$ for therapy duration). The proportions of MTX, LEF, and HCQ in patients with sustained intensive DMARDs were 68.3%, 73.8%, and 61.0%, which were higher than that of non-sustained intensive DMARDs group ($\chi^2 = 19.813$, $P = 0.002$; $\chi^2 = 19.495$, $P = 0.007$; $\chi^2 = 46.027$, $P < 0.001$, respectively) [Figure 1B].

Table 3: Practicability of various remission criteria in daily practice.

Measures	Definition of remission	Practicability
DAS28-ESR	$(0.56 \times \sqrt{SJC28} + 0.28 \times \sqrt{TJC28} + 0.70 \times \ln(ESR) + 0.14 \times PtGA)$	6.4
DAS28-CRP	$(0.56 \times \sqrt{SJC28} + 0.28 \times \sqrt{TJC28} + 0.36 \times \ln(CRP + 1) + 0.14 \times PtGA + 0.9)$	6.8
RAPID-3	(MDHAQ × 3.33 + pain VAS + PtGA)/3 ≤ 1	5.3
SDAI	(SJC28 + TJC28 + PtGA + PhGA + CRP) ≤ 3.3	7.3
CDAI	(SJC28 + TJC28 + PtGA + PhGA) ≤ 2.8	7.0
Boolean	TJC28, SJC28, PtGA, and CRP all ≤ 1	7.5
CliDR	TJC28 = 0, SJC28 = 0, normal ESR and CRP	8.0

CDAI: Clinical disease activity index; CliDR: Clinical deep remission; CRP: C-reactive protein; DAS28-CRP: Disease activity score in 28 joints using CRP; DAS28-ESR: Disease activity score in 28 joints using ESR; ESR: Erythrocyte sedimentation rate; MDHAQ: Multidimensional health assessment questionnaire; PhGA: Physician global assessment (0–10 scale); PtGA: Patient global assessment (0–10 scale); RAPID-3: Routine Assessment of patient index data 3; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint count.

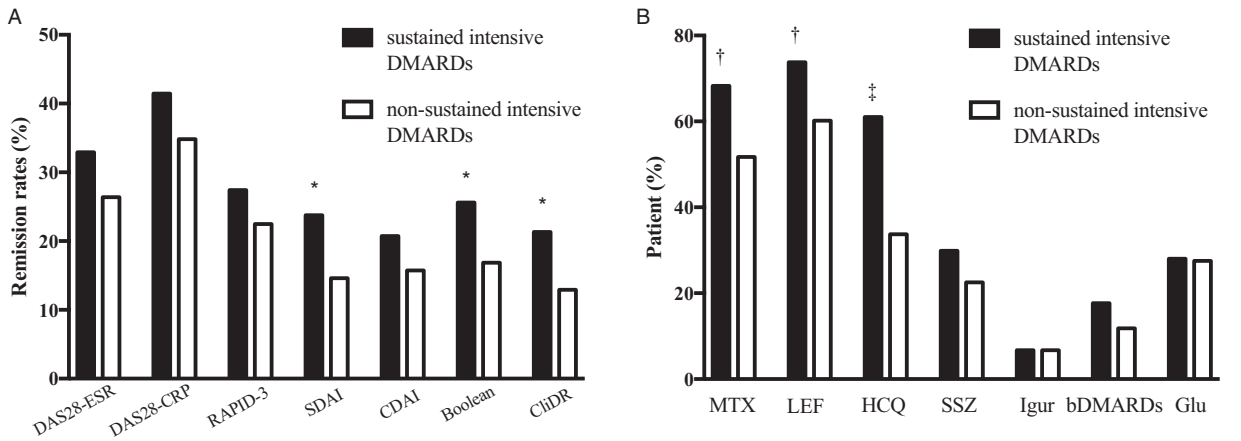

Figure 1: Comparison of remission rates in 342 patients with sustained and non-sustained intensive disease modifying anti-rheumatic drug (DMARD) treatment (A). Proportions of various DMARDs in 342 patients with rheumatoid arthritis with sustained and non-sustained intensive DMARD treatment (B). Glu: Glucocorticoids; Igur: Iguratimod. $^{*}P < 0.05$, $^{\dagger}P < 0.01$, and $^{\ddagger}P < 0.001$ compared with non-sustained intensive DMARD treatment.

Discussion

The most currently recognized remission criteria are DAS28 (<2.6), SDAI (≤3.3), CDAI (≤2.8), RAPID-3 (≤1), and Boolean. However, some of those definitions, such as DAS28, require complex formulas or calculation and cannot be used readily in clinical practice.

As shown by the previous study, most of the patients with RA in remission based on the current definitions showed evidence of residual inflammation.[5,6] Some patients with tender or swollen joints were considered as in remission based on Boolean criteria. It can be argued that these definitions actually reflect minimal RA disease activity rather than remission. Moreover, it has been reported that in those patients with RA with sustained remission based on different criteria for 2 years, some relapsed and had radiologic progression during follow-up.[7,8]

In addition, both SDAI and the Boolean criteria incorporate PtGA into their scores. In fact, PtGA is a limiting factor for remission.[9-11] Patients with RA are frequently afflicted by pain, which may be caused by joint inflammation or non-inflammatory factors, such as osteoarthritis, fibromyalgia syndrome, and so on. Non-inflammatory pain may also confuse PtGA. It is frequently encountered in clinical practice that remission may not be achieved in patients without any visible inflammation because of PtGA.[11] In a study based on the ESPOIR cohort, many patients without visible inflammation did not achieve Boolean remission because of PtGA.[12] The same circumstance was observed in the DREAM remission induction cohort.[23] Obviously, it is difficult for patients to rate an exact score for disease activity.

Our data showed that remission rates according to various definitions were 29.5% for DAS28-ESR, 38.0% for DAS28-CRP, 24.9% for RAPID-3, 19.0% for SDAI, 18.1% for CDAI, 21.1% for Boolean, and 17.0% for CliDR. Remission rates in the current study were similar to or higher than data from previous studies.[24,25] The proportions of remission in the study by Wang *et al*[25] were 8.6% (DAS28), 8.4% (SDAI), 8.2% (CDAI), and 6.7% (Boolean). Data from the multi-center cohort above reflected the average remission in patients with RA of China. However, patients in the current study were recruited from Beijing, where patients were provided relatively better health care. The remission rates were probably expected to be higher than the average of the country. However, compared with data from other countries, remission rates in the current study were still low.[26,27]

Table 4: Effect of treatment on clinical deep remission.

Treatment	CliDR ($n = 58$)	Non CliDR ($n = 284$)	Statistics	P
Duration of therapy (months), media (IQR)	45.0 (22.8–72.3)	30 (9.0–72.8)	−2.295*	0.022
Time from onset to initiation treatment (months), median (IQR)	11.0 (1.8–25.5)	12.5 (2.0–63.5)	−1.368*	0.148
csDMARDs, *n* (%)	58 (100.0)	255 (89.8)	5.222†	0.022
MTX	37 (63.8)	167 (58.8)	0.498†	0.480
LEF	41 (70.7)	187 (65.9)	0.509†	0.476
HCQ	29 (50.0)	131 (46.1)	0.290†	0.590
SSZ	11 (19.0)	78 (27.5)	1.807†	0.179
Iguratimod	4 (6.9)	19 (6.7)	0.003†	0.954
bDMARDs, *n* (%)	7 (12.1)	43 (15.1)	0.364†	0.546
Glucocorticoids, *n* (%)	16 (27.6)	79 (27.8)	0.001†	0.970
Combination therapy, *n* (%)	42 (75.9)	164 (57.8)	4.326†	0.038

Combination therapy was defined as two or more DMARDs combined treatment. *Z values. †χ^2 values. bDMARDs: Biologic disease modifying anti-rheumatic drugs; CliDR: Clinical deep remission; csDMARDs: Conventional synthetic disease modifying antirheumatic drugs; DMARDs: Disease-modifying anti-rheumatic drugs; IQR: Interquartile range; SD: Standard deviation; MTX: Methotrexate; LEF: Leflunomide; HCQ: Hydroxychloroquine; SSZ: Sulfasalazine.

Previous studies showed that antibody against citrullinated proteins (ACPA) was an important predictor for prognosis in patients with RA.[4,28-30] There is a notion that ACPA positive and negative RA are, in fact, two distinct disease subsets.[31,32] The current study did not show differences in remission rates between patients with and without anti-CCP, but those who achieved remission displayed a lower titer of anti-CCP. In addition, some studies reported that negative RF was positively related to remission.[33,34] However, it was not validated in the current or previous studies,[25] which indicated that a negative RF is likely not an independent predictor for remission.

Studies have demonstrated that delay in the initiation of DMARD treatment in patients with RA may lead to a worse outcome than the early start of treatment.[35-37] Patients with earlier DMARDs intervention have a higher likelihood of achieving remission. In the current study, the mean time from RA onset to initiation of the first DMARD treatment was shorter in patients achieving CliDR compared with those who did not, but the difference was not statistically significant. Moreover, patients with sustained intensive DMARD treatment achieved a higher remission rate.

However, none of these csDMARDs was more frequently used in the remission group. It was the treatment duration and combination therapy strictly associated with remission. Intensive treatment using combination DMARDs is proposed to be superior to routine step-up DMARD treatment.[13,38-40] The COBRA and PRINT studies proved that intensive DMARD treatment was an effective treatment strategy for active RA and reached a high response rate.[14] Moreover, the use of csDMARDs combination therapy has been accepted by the new recommendations in the 2016 update.[41] In the present study, we also found that patients with sustained intensive DMARD treatment had higher remission rates based on all seven criteria, especially in the Boolean, SDAI, and CliDR criteria. It might suggest that the Boolean, SDAI, and CliDR criteria were more sensitive at evaluating improvement after treatment.

In conclusion, our study findings indicated that deep remission is achievable in patients with RA. Sustained intensive DMARD treatment is needed to achieve a higher RA remission rate.

Funding

The study was supported by the grants from the National Natural Science Foundation of China (No. 31530020 and No. 81401329) and Beijing Sci-Tech Program (No. Z171100000417007).

Conflicts of interest

None.

References

1. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, *et al*. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001. doi: 10.1038/nrdp.2018.1.
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388:2023–2038. doi: 10.1016/s0140-6736(16)30173-8.
3. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet 2017;389:2338–2348. doi: 10.1016/S0140-6736(17)31491-5.
4. van der Woude D, Young A, Jayakumar K, Mertens BJ, Toes RE, van der Heijde D, *et al*. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. Arthritis Rheum 2009;60:2262–2271. doi: 10.1002/art.24661.
5. Makinen 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.
6. 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.
7. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36–42. doi: 10.1002/art.11481.
8. Lillegraven S, Prince FH, Shadick NA, Bykerk VP, Lu B, Frits ML, *et al*. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. Ann Rheum Dis 2012;71:681–686. doi: 10.1136/ard.2011.154625.

9. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, *et al*. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139–1145. doi: 10.3899/jrheum.111543.
10. Balogh E, Madruga Dias J, Orr C, Mullan R, Harty L, FitzGerald O, *et al*. Comparison of remission criteria in a tumour necrosis factor inhibitor treated rheumatoid arthritis longitudinal cohort: patient global health is a confounder. Arthritis Res Ther 2013;15:R221. doi: 10.1186/ar4421.
11. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–1705. doi: 10.1136/annrheumdis-2012-201519.
12. Aletaha D, Machold KP, Nell VP, Smolen JS. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology (Oxford) 2006;45:1133–1139. doi: 10.1093/rheumatology/kel074.
13. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, *et al*. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347–356. doi: 10.1002/art.10083.
14. 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.
15. Tanaka Y, Hirata S, Kubo S, Fukuyo S, Hanami K, Sawamukai N, *et al*. Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. Ann Rheum Dis 2015;74:389–395. doi: 10.1136/annrheumdis-2013-204016.
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–324. doi: 10.1002/art.1780310302.
17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–2581. doi: 10.1002/art.27584.
18. Prevoo 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.
19. Pincus T, Swearingen CJ, Bergman M, Yazici Y. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol 2008;35:2136–2147. doi: 10.3899/jrheum.080182.
20. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, *et al*. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244–257. doi: 10.1093/rheumatology/keg072.
21. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, *et al*. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–R806. doi: 10.1186/ar1740.
22. 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. Ann Rheum Dis 2011;70:404–413. doi: 10.1136/ard.2011.149765.
23. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HL, *et al*. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology (Oxford) 2012;51:1076–1080. doi: 10.1093/rheumatology/ker425.
24. Lu XY, Li C, Zhao JX, Li ZG. Comparison of ACR/EULAR remission criterion of rheumatoid arthritis published in 2011 year with the other common remission criteria (in Chinese). J Peking Univ Health Sci 2013;45:260–263.
25. Wang GY, Zhang SL, Wang XR, Feng M, Li C, An Y, *et al*. Remission of rheumatoid arthritis and potential determinants: a national multicenter cross-sectional survey. Clin Rheumatol 2015;34:221–230. doi: 10.1007/s10067-014-2828-3.
26. Lutf A, Poil AR, Hammoudeh M. Characteristics of patients with rheumatoid arthritis in Qatar: a cross-sectional study. Int J Rheum Dis 2014;17:63–65. doi: 10.1111/1756-185X.12135.
27. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology (Oxford) 2007;46:975–979. doi: 10.1093/rheumatology/kem007.
28. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: a systematic review. Arthritis Care Res (Hoboken) 2010;62:1128–1143. doi: 10.1002/acr.20188.
29. van den Broek M, Dirven L, Klarenbeek NB, Molenaar TH, Han KH, Kerstens PJ, *et al*. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. Ann Rheum Dis 2012;71:245–248. doi: 10.1136/annrheumdis-2011-200379.
30. van der Woude D, Visser K, Klarenbeek NB, Ronday HK, Peeters AJ, Kerstens PJ, *et al*. Sustained drug-free remission in rheumatoid arthritis after DAS-driven or non-DAS-driven therapy: a comparison of two cohort studies. Rheumatology (Oxford) 2012;51:1120–1128. doi: 10.1093/rheumatology/ker516.
31. van der Helm-van Mil AH, Huizinga TW. Advances in the genetics of rheumatoid arthritis point to subclassification into distinct disease subsets. Arthritis Res Ther 2008;10:205. doi: 10.1186/ar2384.
32. Daha NA, Toes RE. Rheumatoid arthritis: are ACPA-positive and ACPA-negative RA the same disease? Nat Rev Rheumatol 2011;7:202–203. doi: 10.1038/nrrheum.2011.28.
33. Verstappen SM, van Albada-Kuipers GA, Bijlsma JW, Blaauw AA, Schenk Y, Haanen HC, *et al*. A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. Ann Rheum Dis 2005;64:38–43. doi: 10.1136/ard.2003.014928.
34. Forslind K, Hafstrom I, Ahlmen M, Svensson B. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 2007;66:46–52. doi: 10.1136/ard.2006.056937.
35. van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, *et al*. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996;124:699–707. doi: 10.7326/0003-4819-124-8-199604150-00001.
36. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004;43:906–914. doi: 10.1093/rheumatology/keh199.
37. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, *et al*. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446–451. doi: 10.1016/S0002-9343(01)00872-5.
38. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, *et al*. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–3390. doi: 10.1002/art.21405.
39. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, *et al*. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443–1449. doi: 10.1136/ard.2007.071092.
40. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, *et al*. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712–1720. doi: 10.1016/s0140-6736(12)60027-0.
41. Smolen JS, Landewe 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.

How to cite this article: Liu JJ, Li R, Gan YZ, Zhang RJ, Li J, Cai YM, Zhao JX, Liao H, Xu J, Shi LJ, Li J, Li SG, Sun XL, He J, Liu X, Ye H, Li ZG. 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