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

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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 (CiDR), respectively. Boolean and CiDR 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 CiDR 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. A new definition of remission (Deep Remission Criteria, CiDR), which is based on CiDR and DAS28-CRP, was proposed.

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 (DAS28-ESR), Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP), Simplified Disease Activity Index (SDAI), Boolean, and Clinical Deep Remission Criteria (CiDR). CiDR is a combination of DAS28-CRP and Boolean criteria and is considered to be the best definition of remission in terms of practicability scored by rheumatologists (7.5 and 8.0, respectively). The CiDR criteria include low disease activity (DAS28-CRP $<2.6$), Boolean (DAS28-CRP $<2.6$, $\Delta$CRP $<0.5$), SDAI ($\leq 3.3$), and CiDR ($\leq 2.6$), respectively. In this study, we compared the practicability of different definitions of remission of RA and found that CiDR is the best in terms of practicability. 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. A new definition of remission (Deep Remission Criteria, CiDR), which is based on CiDR and DAS28-CRP, was proposed.
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.\(^6\) DAS28-ESR, DAS28-CRP, RAPID-3, SDAI, CDAI, and Boolean were used as described elsewhere,\(^6,18-22\) and clinical deep remission (ClinDR) 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 PhGA 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) |
| PrGA, median (IQR) | 3.0 (1.0–5.0) |
| PhGA, median (IQR) | 2.0 (1.0–4.0) |
| MDHAQ score, median (IQR) | 0.1 (0.0–0.3) |
| 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) |

1 Second hand smoking is included in smoking. 2 0–10 scores. 3 0–3 scores. Anti-CCP: Anti-cyclic citrullinated peptide; bDMARDs: Biological 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; PrGA: Physician observer global assessment; PhGA: Patient global assessment; RF: Rheumatoid factors; SD: Standard deviation; SJC: Swollen joint count; SSZ: Sulfasalazine; TJC: Tender joint count.

### 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 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 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 statistically 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 = 0.003 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       | \((0.56 \times \sqrt{SJC28} + 0.28 \times \sqrt{TJC28} + 0.70 \times \ln(ESR) + 0.14 \times \text{PtGA})\) | 6.4            |
| DAS28-CRP       | \((0.56 \times \sqrt{SJC28} + 0.28 \times \sqrt{TJC28} + 0.36 \times \ln(\text{CRP} + 1) + 0.14 \times \text{PtGA} + 0.9)\) | 6.8            |
| RAPID-3         | \((\text{MDHAQ} \times 3.3 + \text{pain VAS} + \text{PtGA}/3) \leq 1\)                   | 5.3            |
| SDAI            | \((\text{SJC28} + \text{TJC28} + \text{PtGA} + \text{PhGA} + \text{CRP}) \leq 3.3\)         | 7.3            |
| CDAI            | \((\text{SJC28} + \text{TJC28} + \text{PtGA} + \text{PhGA}) \leq 2.8\)                    | 7.0            |
| Boolean         | \(\text{TJC28}, \text{SJC28}, \text{PtGA}, \text{and CRP all} \leq 1\)                    | 7.5            |
| CliDR           | \(\text{TJC28} = 0, \text{SJC28} = 0, \text{normal ESR and CRP}\)                      | 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.

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. 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.

In addition, both SDAI and the Boolean criteria incorporate PtGA into their scores. In fact, PtGA is a limiting factor for remission. 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. In a study based on the ESPOR cohort, many patients without visible inflammation did not achieve Boolean remission because of PtGA. The same circumstance was observed in the DREAM remission induction cohort. 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. The proportions of remission in the study by Wang et al 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. Compared with data from other countries, remission rates in the current study were still low.
Previous studies showed that antibody against citrullinated proteins (ACPA) was an important predictor for prognosis in patients with RA. There is a notion that ACPA positive and negative RA are, in fact, two distinct disease subsets. 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. However, it was not validated in the current or previous studies, 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. 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. The COBRA and PRINT studies proved that intensive DMARD treatment was an effective treatment strategy for active RA and reached a high response rate. Moreover, the use of csDMARDs combination therapy has been accepted by the new recommendations in the 2016 update. 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.

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**Conflicts of interest**

None.

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